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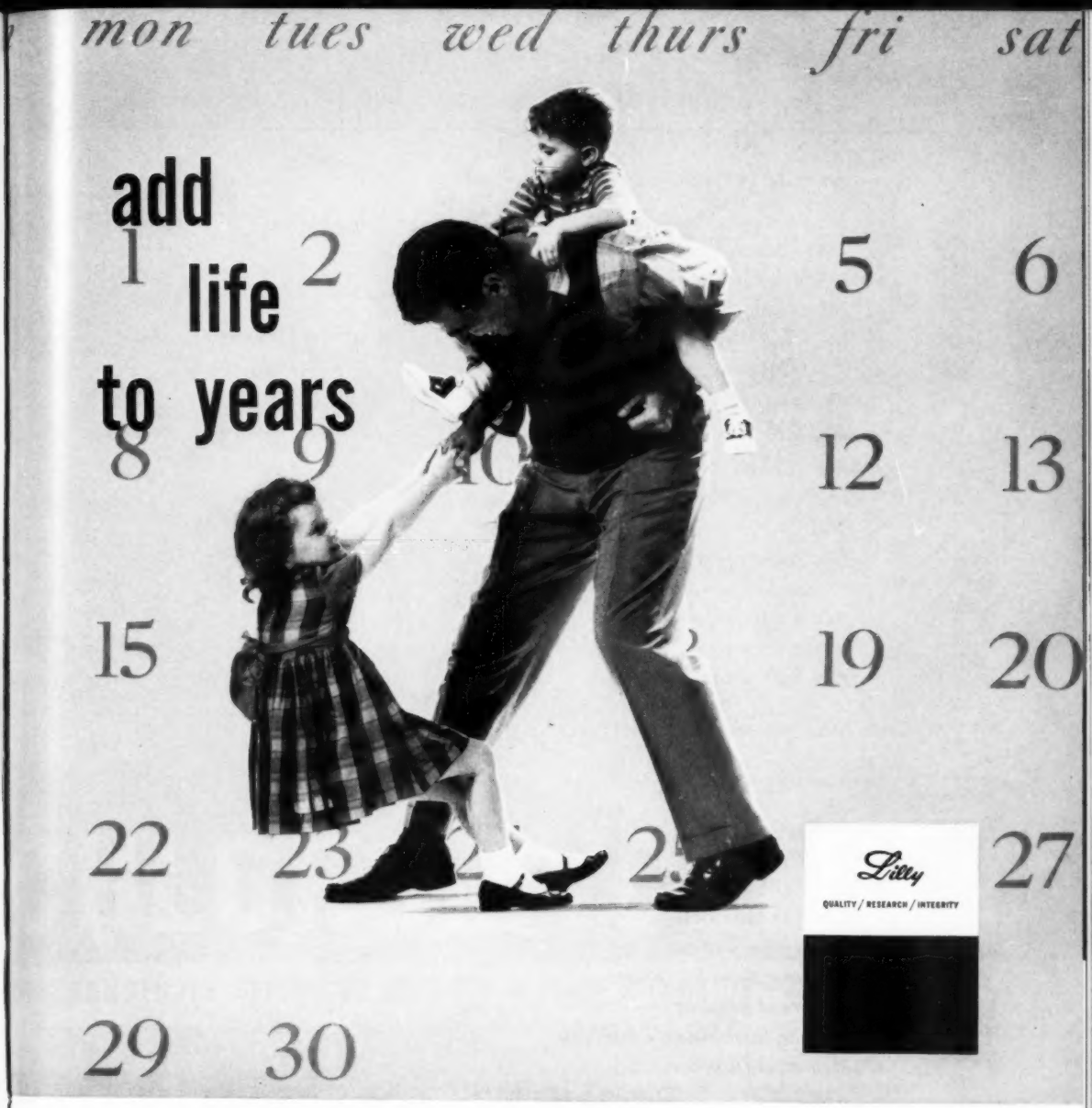

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1. Spies, T. D.: The Influence of Nutritional Processes on Aging, South. M. J., *50*:216, 1957.

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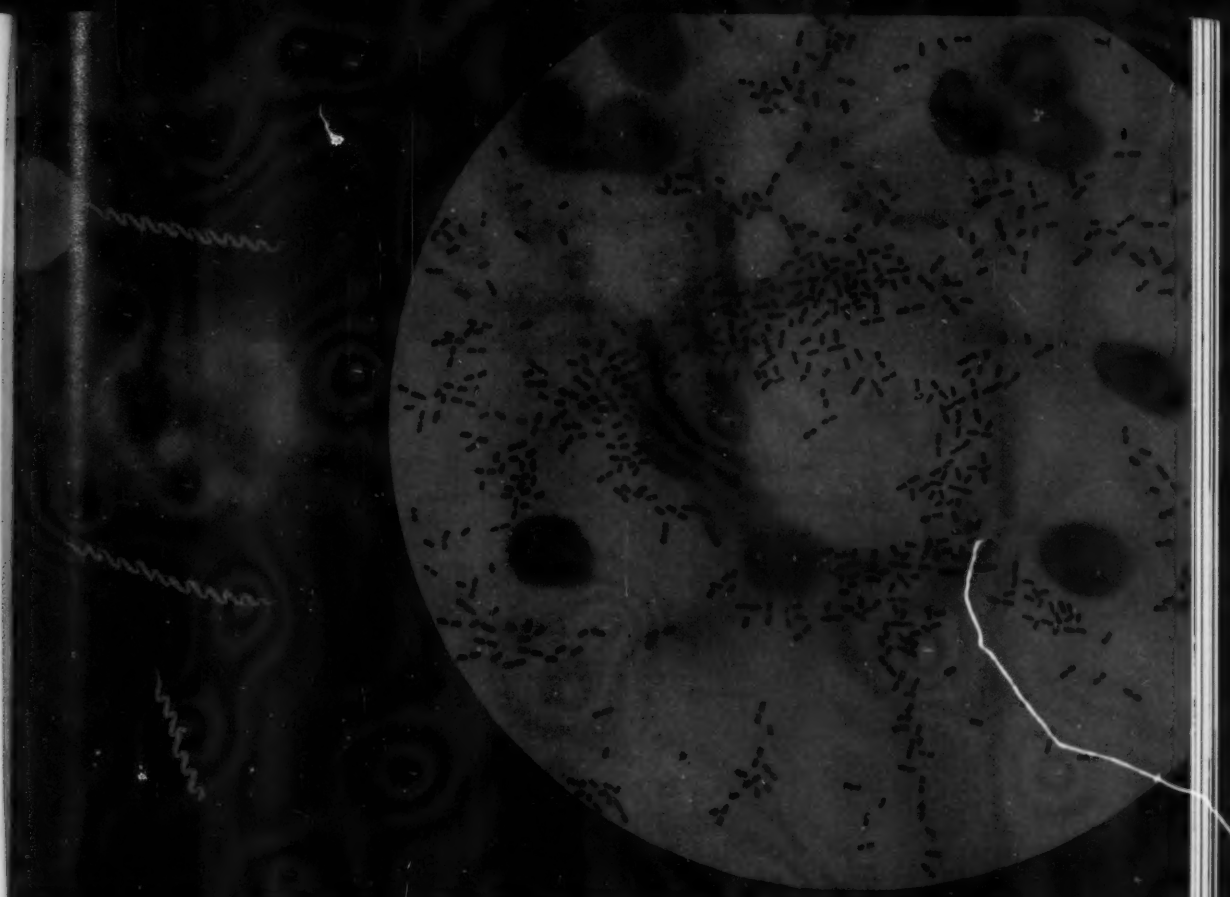

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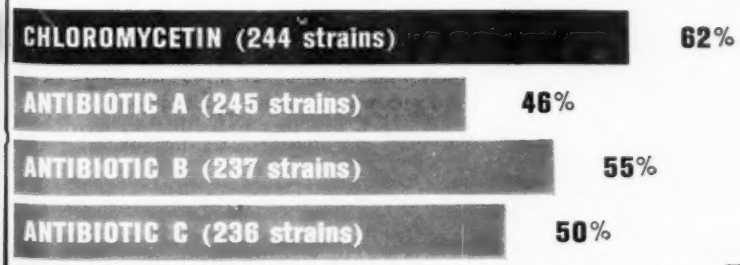
References: (1) Morton, J. J.: *Yale J. Biol. & Med.* **31**:397, 1959. (2) Rogers, D. E., & Louria, D. B.: *New England J. Med.* **261**:86, 1959. (3) Leming, B. H., Jr., & Flanigan, C., Jr., in Welch, H., & Marti-Ibañez, F.: Antibiotics Annual 1958-1959, New York, Medical Encyclopedia, Inc., 1959, p. 414. (4) Edwards, T. S.: *Am. J. Ophth.* **48**:19, 1959. (5) Olarte, J., & de la Torre, J. A.: *Am. J. Trop. Med.* **18**:324, 1959. (6) Suter, L. S., & Ulrich, E. W.: *Antibiotics & Chemother.* **9**:38, 1959. (7) Holloway, W. J., & Scott, E. G.: *Delaware M. J.* **30**:175, 1958.

IN VITRO SENSITIVITY OF GRAM-NEGATIVE ORGANISMS TO CHLOROMYCETIN AND TO THREE OTHER BROAD-SPECTRUM ANTIBIOTICS*



*Adapted from Leming & Flanigan.[3]

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The Editor's Mail

The letter which follows comments on the paper, "The small, frantic voice of the patient," by Mr. William McPeak, which was published in the January issue of POSTGRADUATE MEDICINE. *A carbon copy of the letter was sent to the Editors, who felt it would be of interest to readers of the Journal and are publishing it with the writer's permission.*

Mr. William McPeak
The Ford Foundation
New York, New York

Dear Mr. McPeak:

It is with some interest that I read your article entitled "The small, frantic voice of the patient" in POSTGRADUATE MEDICINE for January 1960. The title caught my attention. The subject matter in some respects stirred my ire, and I am tempted to title this "The small, frantic response of the doctor."

Your first patient-voiced criticism stems from crowded waiting rooms. Now, I have often wondered if anyone considered the opposite situation. I have had all patient visits on appointments for 17 years. To keep such a schedule necessitates spending more than the usual three to five hours in the office. My shortest stay is five hours of appointments; this does not include preliminary setting up of my instruments, sterilization, answering correspondence, filling out insurance reports, etc. I am helped by my secretary, but I spend a minimum of one and a half hours on this latter chore daily. Without hospital rounds and surgery, this adds up to quite a few hours. So you see, having a schedule of definite appointments takes more of the doctor's time.

Now, what is the reaction of patients? Most of them "love" it. But—there is often the patient who is late (we forgive lateness of five minutes); any patient consistently late (three times) is refused further appointments. Then there is the occasional patient who "forgets" an appointment; when this occurs three times, he cannot get another appointment. There is the patient who comes in at the wrong time and the wrong day and insists that is his appointment time (and always *without* our written appointment slip to corroborate the appointment). There is occasionally the patient who never comes in for his appointment (this is bad with new patients who are scheduled for 45 minutes). Old patients who failed to come in always "forget" it or "postpone" it without notifying us (our slip states they should notify us 24 hours in advance if unable to come in).

Then there is the patient—new or old—who comes in without an appointment, is not acutely ill (we always find space for these), and wants to be seen. He is told we cannot give somebody else's time to him; that we will gladly see him at the end of the list. It would be instructive to you to see these people (*occasionally*) storm out of the office with some unprintable remark (and they were so ingratiating a moment before). And, believe me, they are talked to in the nicest way possible. In addition, there are some who call just a few minutes before their appointment to say they cannot make it because they missed the bus, the car is stalled, the husband didn't arrive to take them, etc.

I know of a few doctors who have made a serious effort to see patients on appointment. Because of some of the reasons listed, they became discouraged and ceased such an arrangement.

I will skip your statement that it is difficult to get old x-rays of patients transferred to a new doctor. The usual difficulty lies in the fact that x-rays are held only a few years (five years at our hospital). I have never had trouble getting old x-rays of patients, with one exception, and that is from federal hospitals.

Regarding house calls, our staff has subscribed to (and advertised, at one time) the idea of having newly located people in a community see a local general practitioner and get acquainted. He will not let them down when they are so ill that they cannot come to the office. It would be most amusing to you to hear a general practitioner's discussion of the necessity of most house calls.

Regarding your statement that "our present systems of health insurance . . . often provide no benefits for nonsurgical cases unless hospitalized," I am one who is convinced that only a serious illness (i.e., one that needs hospitaliza-

(Continued on page A-22)

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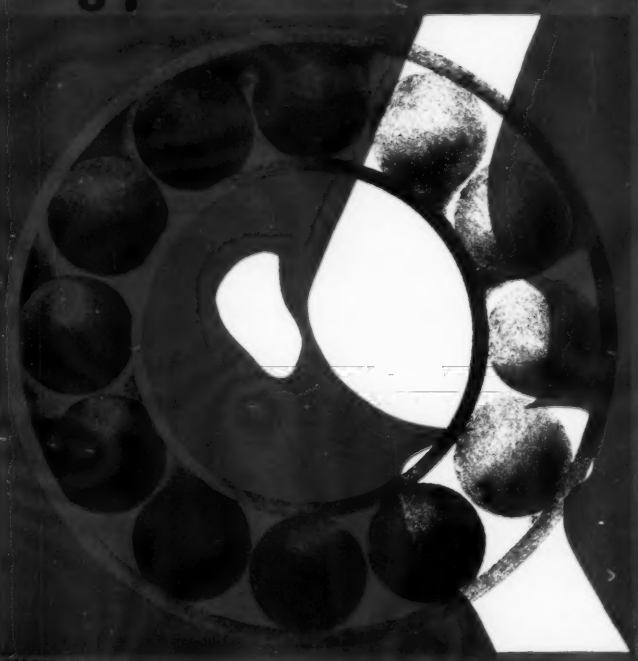

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PM-4-60

tion) should carry medical coverage. I am convinced that no insurance policy should cover medical office or home visits. With only a rare exception, people can afford to pay for an office or home visit. My attitude stems from a primary conviction that some private responsibility should be left to each person to maintain his physical and mental welfare. I am opposed to the innumerable industrial medical care plans that include payment for office or home visits. People are, thereby, *conditioned* to total medical care and such conditioning is easily transferred as a responsibility to the government. People have a more rational approach to auto insurance than medical insurance. The inclusion of a first payment of $25 to $50 per year by the individual in a medical plan (before the insurance carrier becomes responsible) is hardly a demonstration of private responsibility in a person earning $5000 to $7500 yearly (I am thinking of two local arrangements). To top it all, this initial payment includes the cost of BAND-AIDS®, aspirins, etc. purchased at the local drugstore.

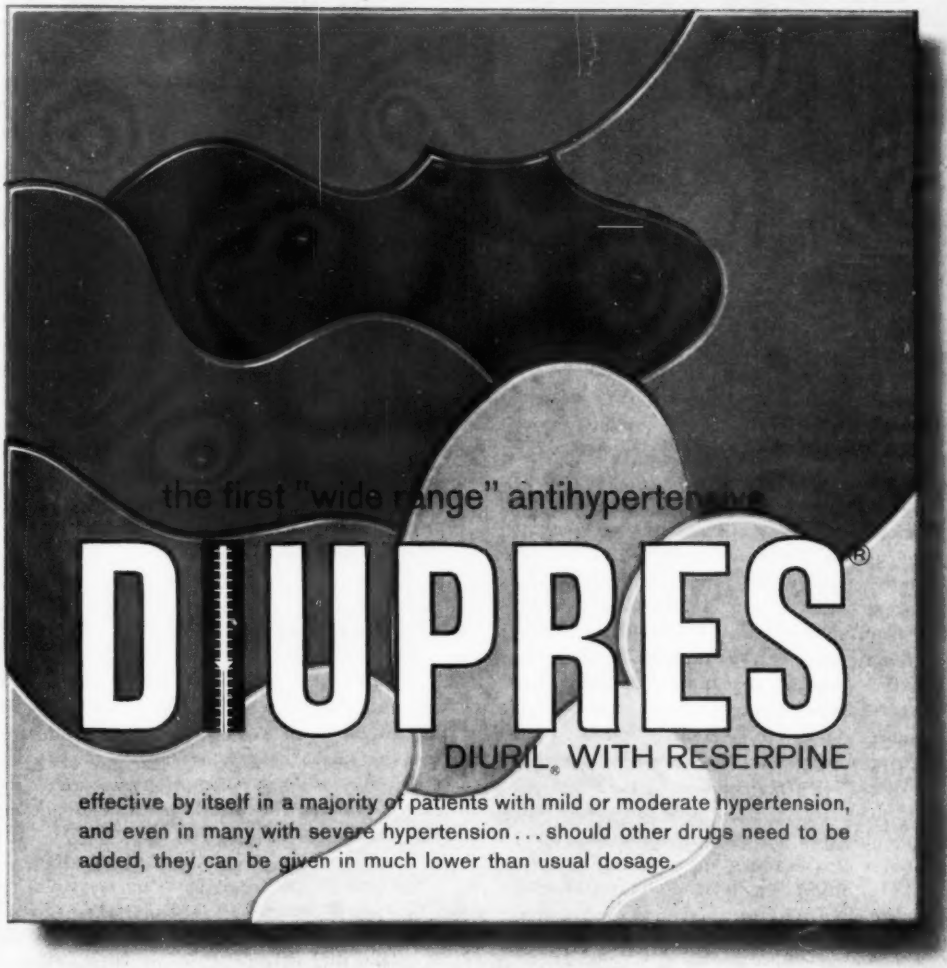
I am going to skip several complaints and take issue with you in your statement, "Not always but frequently the choice of procedure involves the choice to collect a higher or lower fee, or none at all." I am ashamed of your insinuation. In our medical school days, in our internship and residency, indications and contraindications of various procedures have been emphasized and harped on. I am aware that we are not 100 per cent Simon-pure, but I am ashamed that you use this argument for clinic care.

I had hoped that the reliability of polls (surveys) would be questioned by more people.

Your statement that doctors ignore charitable appeals and evade some of their income tax is true; but how often? How rampant is the practice? I am indeed sorry that you have so little faith in your fellow beings. Perhaps, this is more common than people realize, and fits in with the degradation of the moral fiber of our people so noticeable in the last 20 to 30 years. . . .

Doctors, as a group, have been the object of so many bitter, usually unjustified, generalized attacks, that I have often wondered about the source of such criticism. You have mentioned in your article some of these complaints. Perhaps, my remarks have slightly shaken your belief in their soundness.

Sincerely yours,
Edward Palmer, M.D.
Berwyn, Illinois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Your Questions answered

** Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants. Replies are forwarded by mail immediately and selected questions and answers are published each month in this section.*

• VITELLINE DUCT LESION

Q. A 14 day old girl has an apparent remnant of the omphalomesenteric duct protruding from the center of the umbilicus. The cord stump detached itself spontaneously on the eighth day after birth. A bright red, moist cylindrical projection could then be seen arising from the center of the umbilicus. It measured approximately 1 cm. in height and 2 mm. in diameter. The distal end appeared to taper and there was no opening or discharge. No masses or tenderness could be found in the region of the umbilicus. The projection appears to be an omphalomesenteric polyp.

This lesion was touched with silver nitrate and kept as aseptic as possible. The surrounding area is perfectly normal and dry at present. The baby's growth and development are normal and the only other finding appears to be a small lipoma of the scalp. The father was operated on when he was two weeks old for a malrotation of the intestine.

Should the superficial lesion be removed by itself, or should an exploratory laparotomy be done to make sure this lesion is not connected to the ileum, a condition which would cause future complications? If surgery is indicated, when should it be performed?

M.D.—Illinois

A. The polypoid lesion presenting at the umbilicus probably represents the persistence of part of the vitelline duct. It is quite possible that there is a connection between the inner surface of the umbilicus and the ileum, even though no ileal contents have drained from the navel. I think it would be best to explore the inner surface of the umbilicus at the time the lesion is removed to be certain that no remnant of the vitelline duct is present which could later serve as a source of intestinal obstruction. This can be done by making a short transverse incision just caudad to the umbilicus, separating the two rectus muscles at this point and opening the peritoneum. If some connection is found between the ileum and the umbilicus it can be severed, and any opening in the ileum can be closed. This procedure will divide the urachus. The polypoid projection at the umbilicus can be removed.

This operation can be performed as soon as the baby is in good condition.

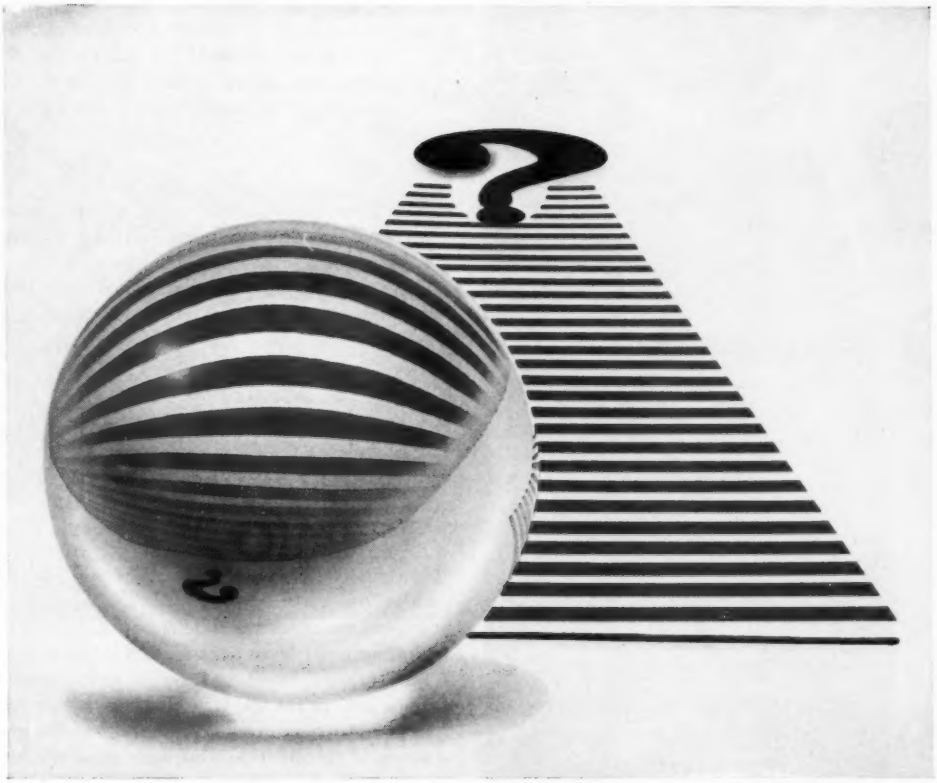
• VACCINATION TAKES

Q. A nine month old girl has been vaccinated five times without success. Fresh vaccine has been used each time and has been obtained from two drug companies. The acetone used to cleanse the arm was allowed to dry completely before scarification was done. How may I get a positive take on this child?

M.D.—Indiana

A. No one is sure why this frustrating experience occurs, but time and perseverance are almost always rewarded by an eventual take. When technics and materials are good, it is assumed that an unusually persistent passive immunity or delayed motivation of the baby's own immunochemical pathways are factors. It is interesting that babies with agammaglobulinemia respond to smallpox vaccination and sometimes violently so. I suggest that this baby be revaccinated at one to three month intervals. The technics described are correct.

(Continued on page A-28)



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References: 1. Dowling, H. F.: Postgrad. Med. *23*:594 (June) 1958. 2. Gimble, A. I.; Shea, J. G., and Katz, S.: Antibiotics Annual 1955-1956 New York, Medical Encyclopedia Inc., 1956, p. 676. 3. Long, P. H., in Kneeland, Y., Jr., and Wortis, S. B.: Bull. New York Acad. Med. *33*:552 (Aug.) 1957. 4. Rein, C. R.; Lewis, L. A., and Dick, L. A.: Antibiotic Med. & Clin. Ther. *4*:771 (Dec.) 1957. 5. Stone, M. L., and Mersheimer, W. L.: Antibiotics Annual 1955-1956, New York, Medical Encyclopedia Inc., 1956, p. 862. 6. Campbell, E. A.; Prigot, A., and Dorsey, G. M.: Antibiotic Med. & Clin. Ther. *4*:817 (Dec.) 1957. 7. Chamberlain, C.; Burros, H. M., and Borromeo, V.: Antibiotic Med. & Clin. Ther. *5*:521 (Aug.) 1958. 8. From, P., and Alli, J. H.: Antibiotic Med. & Clin. Ther. *5*:639 (Nov.) 1958.

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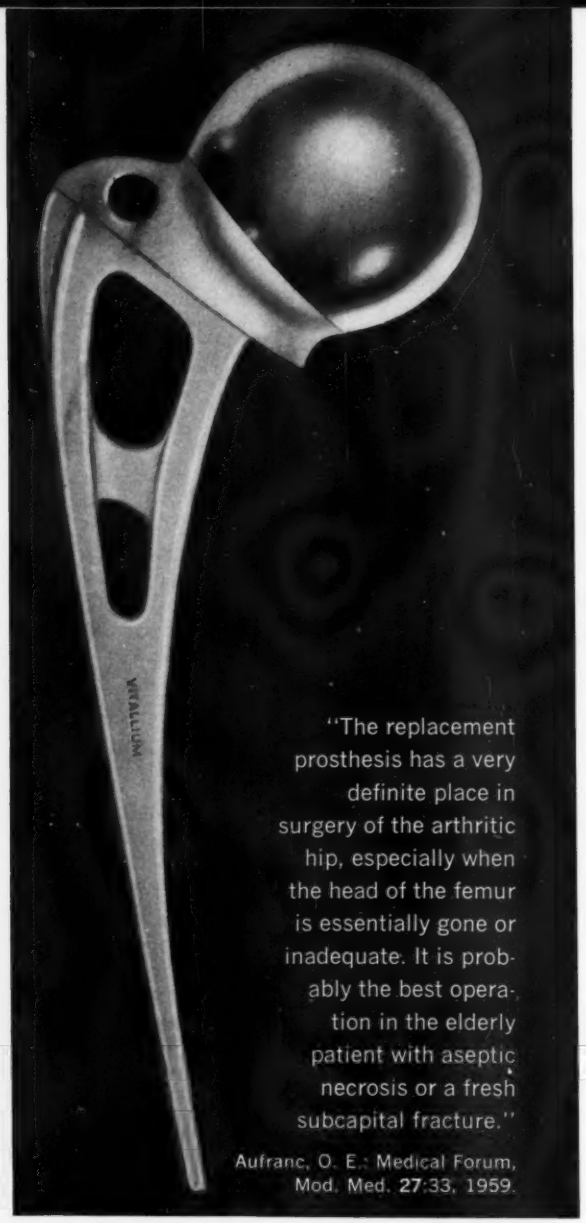

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Aufranc, O. E.: Medical Forum, Mod. Med. 27:33, 1959.

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Literature on request

• IMMUNIZATIONS FOR INFANTS

Q. What is the preferred schedule of immunizations for infants, including diphtheria, whooping cough, tetanus and polio? I would also like to know the most advisable time to start immunizations and how frequently booster doses should be given.

M.D.—Ohio

A. There is some difference of opinion about an ideal schedule of immunizations. With quadruple vaccine, many pediatricians give immunizations at three, four and five months, followed by booster doses administered at 12 months and at two years of age.

• ABNORMAL BRUISING

Q. A 14 year old boy who started playing football this year sustained in contact large, painful bruises which covered a good part of his body. He had far more bruises than the average number received in this sport. Routine blood and urine studies yielded normal findings. A smear showed an adequate platelet count. Bleeding and clotting times were normal, and a tourniquet test for increased capillary fragility gave negative results. Except for the large bruises, which seemed to be absorbing normally, findings of the general physical examination also were noncontributory.

Can this boy safely continue to play football? Does this condition indicate an increased susceptibility to similar damage to internal organs?

M.D.—Nebraska

A. The fact that this boy has normal coagulation and bleeding times and a normal platelet count does not exclude the possibility that one of the hemorrhagic diatheses may be present. These tests are crude and may not be sufficiently sensitive to indicate coagulation defects.

The familial history should be carefully reviewed for other instances of persons with tendencies toward bleeding. In addition, special coagulation studies, such as the thromboplastin generation and prothrombin time tests, should be carried out.

In view of the history of extensive ecchymoses, the patient should not indulge in any of the potentially traumatic sports, regardless of laboratory findings.

(Continued on page A-30)

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1. Mintz, A. A.: Management of the Febrile Child, J. Ky. Acad. Gen. Pract. 5:26 (Jan.) 1959.

• CHRONIC INTERMITTENT PORPHYRIA

Q. A 45 year old man with multiple aching pains has leukocytosis and an elevated uric acid level. A diagnosis of chronic intermittent porphyria has been made. Is there any definitive effective treatment for this condition?

M.D.—Wisconsin

A. A number of treatments have been recommended for chronic intermittent porphyria, including the utilization of cortisone and, more recently, the so-called chelating agents. Thus far, these treatments have not proved very effective and I cannot recommend them to you with any degree of optimism. May I suggest that every effort be made to verify the accuracy of the original diagnosis, since if you can prove some other cause for the abdominal pains, you may then be able to effect a more satisfactory treatment.

• MENSTRUAL DISORDERS

Q. As a staff physician in a university health center, I see many girls with menstrual disorders such as irregularity, menorrhagia, metrorrhagia and apparent cessation (several months without menses). How should these problems be evaluated? I have been criticized by older physicians for doing a pelvic examination because many of the girls are virgins. In the presence of metrorrhagia, should dilatation and curettage be done at the start of treatment? Should Papanicolaou smears be done routinely, or is cyclic therapy indicated?

M.D.—Utah

A. The physician should exercise judgment in managing menstrual disorders in girls of this age, and treatment should be individualized. A rectal examination should be performed in all patients who have amenorrhea in order to rule out a possible pregnancy or a gross pelvic abnormality. Inspection of the external genitalia will indicate the advisability of a vaginal examination. In cases of abnormal bleeding, a Papanicolaou smear should be made from the vaginal secretions. After the preliminary examination, cyclic therapy may be tried. If this fails to control the irregularity, diagnostic curettage should definitely be performed to determine whether or not a malignant lesion is present. Again, I would recommend individualization of these problems.

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DRUG THERAPY IN TONSILLECTOMIES

American Laryngological, Rhinological and Otological Society, Southern Section:

• In a series of 100 patients undergoing tonsillectomy and adenoidectomy, antimicrobial agents were used to control or reduce clinical evidence of inflammation. A control group of 40 patients did not receive the treatment. Tissues taken from the excised organs were free of pathogens in only 10 patients in the study group and in four patients in the control group. This should not minimize the importance of looking for clinical symptoms of bacteremia before and after tonsillectomy and adenoidectomy. However, antimicrobial agents should be given for specific indications rather than as a routine procedure.—Dr. Peter N. Pastore, Medical College of Virginia, Richmond.

• In 20 patients, a perforated eardrum was corrected with vein grafts taken from the hand or foot. Such grafts heal faster than do skin grafts removed from the inner surface of the eardrum and are easier to obtain.—Dr. Harold G. Taub, Tulane University School of Medicine, New Orleans.

RECRUITING MEDICAL STUDENTS

Federation of State Medical Boards of the United States:

• To obtain better medical students, there should be more personal contact by practicing physicians. Each of us should make it our responsibility to encourage a talented student toward a medical career. We must persuade states and some of the private schools to ease their rigid geographical restrictive policies for admission. I favor scholarships for beginning medical students. The possibility of adequate loans to finance students' medical education also should be studied. More realistic financial arrangements for residents in training must be found. In my opinion, residents should receive an annual stipend of $8000 to $9000 for the medical services they render.—Dr. Louis M. Orr, Orlando, Fla.

BUTTOCK INJECTION PERILOUS IN NEWBORN

American Federation for Clinical Research, Southern Section:

• Intramuscular injections of therapeutic agents in newborns should be made into the midanterior thigh. Twelve cases of injury to the sciatic nerve in infants have been recorded following injection into the buttock. The lower limb deformities originally had been attributed to poliomyelitis or congenital clubfoot. All the children had received antibiotics. In most instances, recovery was poor. The neuropathy was produced in newborn rats. The syndrome apparently is initiated by chemical irritation and not by needle trauma.—Dr. Mollie Combes, University of Texas Southwestern Medical School, Dallas.

Cadavers are chief Russian blood source

Fourth Biennial Conference on Homotransplantation:

- Six to 8 pt. of blood may be obtained from cadavers within 10 hours of death due to accidental or noninfectious causes. Four-fifths of all blood given at a Moscow institute is obtained through this source. The blood does not clot and does not require chemical additives. It is usable for five weeks if properly refrigerated.—Dr. Mikhail M. Tarasov, Sklifosovsky Institute, Moscow.

Drug prices proportionately lower

Central Regional Conference, Pharmaceutical Manufacturers Association:

- Prices of drugs have not increased disproportionately to the cost of other goods and services. On the contrary, prices of specific new products, such as the steroid hormones which were introduced at prices necessarily higher than those of some of the older drugs, have declined in 10 years. This has happened in a period of rising prices for almost every other commodity.—Dr. E. Gifford Upjohn, Kalamazoo.

Inconsistent mother has disciplinary problem

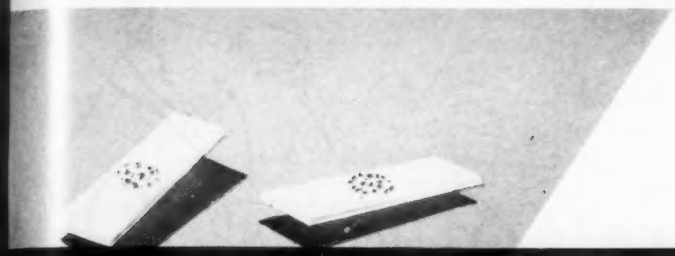
American Orthopsychiatric Association:

- The mother who disciplines inconsistently is the most frequent type seen at child guidance clinics. Her child acts out antisocially to test limits. Disobedience is the key problem. Typically, the inconsistency of the mother arises because she equates discipline with hostility. She is unable to administer discipline effectively because of her guilt. Treatment aimed specifically at freeing the mother of this guilt often produces dramatic improvement.—Dr. Maurice J. Rosenthal, Institute for Juvenile Research, Chicago.
- Although overt manifestations of depression are rare in children and adolescents, depressive feelings and "depressive equivalents" are commonly encountered. These include fatigue, boredom, restlessness and difficulty in concentration. Such children seek constant stimulation by means of talking, parties, telephoning and the radio, and respond to each passing fad. Exploration of fantasy life and dreams may be valuable in recognizing depression in youngsters. Their dreams often will be of dead persons beckoning to them or of horrible deeds being done to themselves.—Dr. James M. Toolan, Bellevue Hospital, New York.

Transplantation immunity after irradiation

Society of University Surgeons:

- Whole body irradiation has been applied to five patients. The x-ray dose has ranged from 200 r to 700 r, with bone-marrow support in two patients. Kidney homotransplantation was performed in three patients and skin homotransplantation in a fourth. One patient has survived for more than 10 months following an x-ray dose requiring no bone-marrow support, kidney transplantation from a nonidentical twin brother, and bilateral nephrectomy. The other patients died within 35 days of irradiation.—Dr. Joseph E. Murray, Peter Bent Brigham Hospital, Boston.
- Resistance to transplantable rat tumors has been achieved in animals that have recovered from an inoculation with FHA, a filterable agent causing acute hemolytic anemia. The results demonstrate for the first time the production of resistance to cancer by an infectious agent completely separable from the tumors. Studies are in progress on the cytotoxic effects of FHA antiserums on malignant cells.—Dr. J. H. Sacks, Medical College of Virginia, Richmond.



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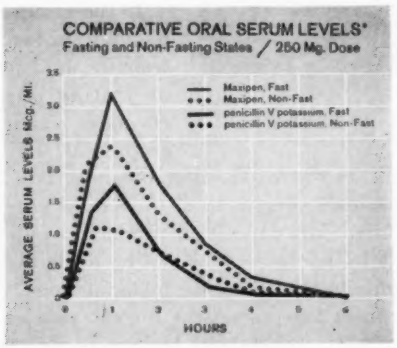

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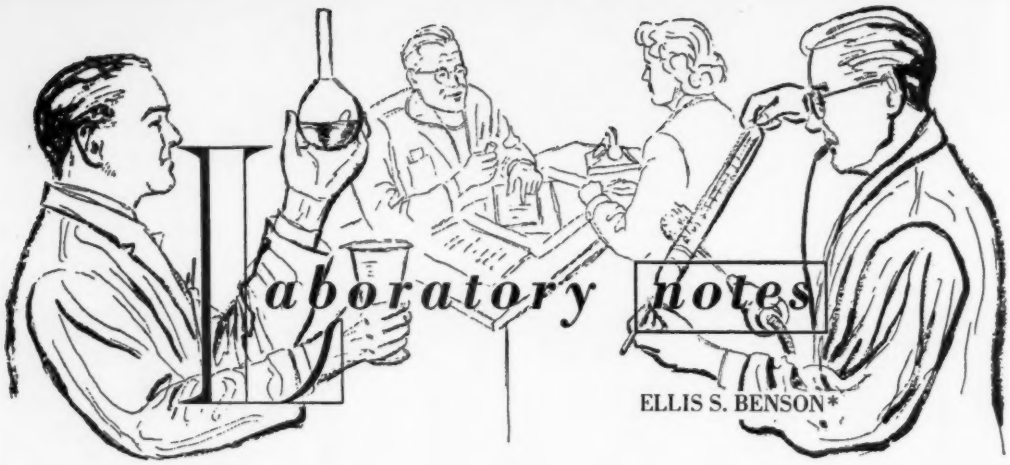


Use of Morphologic Histochemical Technics for Demonstrating Enzymes

LEE W. WATTENBERG

University of Minnesota Medical School, Minneapolis

Dr. Wattenberg has pioneered an effort to utilize knowledge and technics of enzymology in the field of pathology with particular emphasis on the distinctions between neoplastic and normal cells. In addition to its clinical ramifications, this approach may give us fundamental knowledge concerning cancer cells, their growth and metabolism. Dr. Wattenberg, a biochemist as well as a pathologist, is currently Hill Foundation Professor in Morphologic Histochemistry in the Department of Pathology at the University of Minnesota Medical School.—Ellis S. Benson, M.D.

In recent years a new interdisciplinary area, the morphologic histochemical demonstration of enzymes, has been rapidly expanding, and at the present time these technics are beginning to be applied to problems of clinical medicine.

Morphologic histochemistry encompasses a group of technics which make it possible to visualize the site of specific chemical entities in a microscopic section. Whereas classic staining methods give only morphologic detail, histochemical procedures supply information pertaining to both the chemical composition and the morphologic properties of the tissue components.

LEE W. WATTENBERG

In the group of morphologic histochemical technics used for demonstrating enzymes, chemical reactions are employed which result in the production of some type of an insoluble compound at the site of enzyme activity. This deposition product is either visible by microscopy or can be made visible by some further chemical manipulations. In general, in the procedures for carrying out such technics, a histologic section is placed in an incubation medium containing the specific substrate for the enzyme, a buffer, inorganic salts, and a histochemical reagent. This reagent is usually soluble in the unaltered incubation medium. However, as a result of

(Continued on page A-49)

*Director of Hospital Laboratories and Associate Professor of Clinical Medicine and of Pathology, University of Minnesota Medical School, Minneapolis, Minnesota.

the activity of the specific enzyme being studied, it participates in the formation of an insoluble deposition product at the site of the enzyme. For example, in the procedure for demonstrating acid phosphatase, beta-glycerophosphate serves as the substrate. The histochemical reagent present in the reaction mixture is a lead salt. As a result of phosphatase action, the phosphate group is hydrolyzed from beta-glycerophosphate. Lead phosphate, being a highly insoluble salt, precipitates close to the site of enzyme activity. Unfortunately, lead phosphate is not readily visible, but this salt can be converted to the black lead sulfide by addition of hydrogen sulfide. Thus, in a microscopic examination of such a preparation, a black deposit would indicate the site of acid phosphatase in the tissue section.

The years 1938 and 1939 marked the beginning of the modern era in the morphologic histochemical demonstration of enzymes. Prior to this time, a few enzymes could be demonstrated by such technics, but these procedures offered relatively little to the pathologist. Takamatsu (1938) and Gomori (1939) almost simultaneously published methods for demonstrating alkaline phosphatase. These publications excited the interest of numerous scientists, and in the subsequent years intense efforts were made to determine the validity of the phosphatase technics and to expand the number of enzymes that could be demonstrated by similar methods. In the next few years, a great deal of experience was obtained in methodology, in interpretation, and in evaluating potential pitfalls of these procedures. However, because the particular group of enzymes which were available for study at that time were for the most part of relatively little clinical interest, only minimal applications of these technics to the clinical field were attempted.

Following this early exploratory period in enzyme histochemistry, a comparatively large number of technics for demonstrating enzymes were developed. These included technics for demonstrating hydrolytic enzymes such as aminopeptidase, β-glucuronidase, glucose-6-phosphatase, and many others. In addition, it became possible to demonstrate a considerable number of oxidative enzymes by employing a group of reagents called tetrazolium salts. These compounds have the remarkable property of being almost colorless and water-soluble in the oxidized form and of becoming highly colored and highly insoluble in the reduced form. Their oxidation-reduction potential is such that a number of enzyme reactions occurring in biologic systems will cause them to be reduced. Enzymes which fall into this category are succinic dehydrogenase, α-glycerophosphate dehydrogenase, enzymes of the mitochondrial electron transport system, and miscellaneous oxidases such as monoamine oxidase. With the tetrazolium salts, it is also possible to demonstrate indirectly a whole sequence of enzymes in which either coenzyme I or coenzyme II is reduced. It is accordingly possible in this manner to demonstrate enzymes such as lactic dehydrogenase, malic dehydrogenase and certain enzymes concerned with steroid metabolism such as steroid 3β-ol dehydrogenase.

Compared to classic staining procedures, morphologic histochemical technics for demonstrating enzymes have three advantages: (1) These technics are in general more sensitive than are the classic staining procedures; (2) it is possible to use morphologic histochemical technics as a means of demonstrating the metabolic or functional relationships between cells and in some cases in identifying the cell type; and (3) since histochemical technics give biochemical information, they can be used to elucidate the basic mechanisms involved in pathologic processes.

An example of the use of morphologic histochemical technics for demonstrating enzymes as a sensitive technic for showing early pathologic changes was published by Wachstein and Miesel in 1955. These authors reported that changes in the activity of oxidative enzymes occur very soon after myocardial infarction; in some instances, such changes precede any observable alterations which can be demonstrated by classic staining procedures. It should be pointed out, however, that sensitivity has certain disadvantages. Procedures which are highly sensitive to incipient pathologic alterations likewise may be sensitive to factors af-

(Continued on page A-50)

fecting cells but not related to in vivo pathologic conditions and accordingly must be carefully standardized.

Many differences exist in the enzymatic composition of cells. This is particularly true of enzymes with highly specialized functions. In some instances, advantage can be taken of such enzymatic characteristics to demonstrate a relationship between cells which otherwise would not be apparent. An example of this usage of enzyme histochemistry is the application of the procedure for demonstrating aminopeptidase to the study of the relationship between gastric metaplasia and carcinoma of the stomach. In many older individuals, normal gastric glands in some areas of the gastric mucosa are replaced by glands resembling those found in the small intestine. In patients with gastric carcinoma, this intestinal metaplasia is particularly prominent in many instances. Considerable attention has been given to the question of whether gastric malignancies arise from this metaplastic epithelium or from gastric glands. By employing the histochemical procedure for demonstrating the enzyme aminopeptidase, it has been possible to show that the cells of the mucosa of the normal small intestine have intense aminopeptidase activity. Likewise, the cells found in intestinal metaplasia of the gastric mucosa have intense activity; furthermore, in approximately 30 per cent of gastric carcinomas, cells with intense aminopeptidase activity are found. Since gastric glands do not show positive aminopeptidase activity, these data would suggest that a distinctive interrelationship exists between intestinal metaplasia and those gastric carcinomas in which aminopeptidase-positive cells are present.

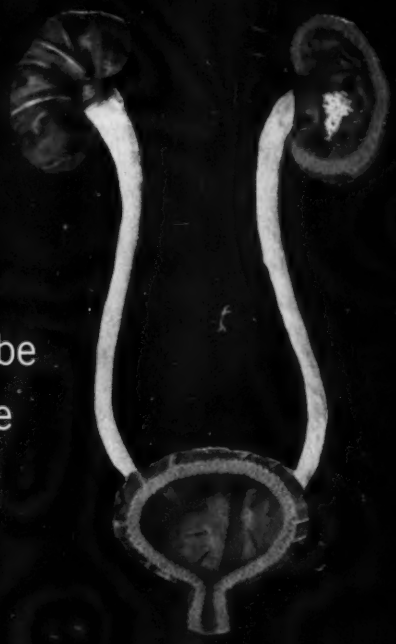
Although high sensitivity to pathologic changes and accurate determination of cellular relationships are important, by far the greatest potential of enzyme histochemistry is in delineating actual mechanisms of disease. In this realm histochemistry must be thought of not simply as a morphologist's tool but as a branch of biochemistry which has an almost unique contribution to make, namely, the ability to localize the specific site of a particular biochemical event.

Even casual histochemical studies reveal a marked heterogeneity in the enzyme properties of the various cellular components of almost every tissue. Thus, the liver, which is frequently thought of as tissue in which the great majority of the cells are uniform, turns out to be considerably more heterogeneous than might be anticipated from its morphologic appearance. Not only do the biliary radicles react differently than do the hepatic cord cells, which might be expected, but within the liver lobule are found remarkable differences in the enzyme composition of the cells of the hepatic cords. For example, the activity of DPN diaphorase, an enzyme related to electron transport, is very intense in the hepatic cells in the central areas of the lobules. In contrast, in the periportal portion of the lobules, the activity of this enzyme is relatively weak. This suggests that these cells about the central veins have a different intermediate metabolism, compared with the cells in the vicinity of the portal triads. Conventional biochemical procedures which might be carried out on liver homogenates would include cells with markedly diversified metabolic properties, and, in fact, in many instances would not give any more specific information than would a study carried out on two or more separate organs. The difficulties which exist in applying conventional homogenate technics to obtain information as to biochemical changes due to a disease process in such an organ immediately become apparent. With morphologic histochemical procedures which localize the site of enzyme activity, heterogeneity ceases to be an impediment; in some instances, by giving morphologic relationships as well as biochemical data, it may be an actual advantage.

Recently, morphologic histochemical studies of oxidative enzymes in normal and proliferative lesions of the large bowel in man have been reported. Like the liver, the normal mucosa as well as proliferative lesions of the mucosa of the large bowel are composed of epithelial cells in which enzyme activities differ. It has been shown, for example, that the cells at the base of the glandular crypts of normal large bowel mucosa, hyperplastic mucosa,

(Continued on page A-52)

Just a "simple" case of cystitis may be the precursor of pyelonephritis[1]— or may actually be the first evidence of a pre-existing pyelonephritic process.[2]



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REFERENCES: 1. Campbell, M. F.: Principles of Urology, Philadelphia, W. B. Saunders Co., 1957. 2. Colby, F. H.: Essential Urology, Baltimore, The Williams & Wilkins Co., 1953.

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and benign adenomatous polyps have a high succinic dehydrogenase activity. In other cells of these normal and pathologic tissues, the succinic dehydrogenase and cytochrome oxidation activities tend to parallel one another; in the basal cells the cytochrome oxidase activity does not show a high activity comparable to that of succinic dehydrogenase.[1] This suggests that basal cells have some unique metabolic property related to succinate oxidation. Since these cells define the depth to which glands penetrate, this metabolic pattern may play a role in determining the benignancy or malignancy of a particular lesion. Thus, in malignant adenomatous polyps a low succinic dehydrogenase activity is found in the basal areas of the atypical glands which are present in these lesions. Similarly, in manifestatively infiltrating carcinoma a low activity of this enzyme is observed.

Histochemical studies of proliferative lesions of the large intestine have revealed other interesting findings. A histochemical reaction pattern, distinct from the patterns found in normal mucosa or benign neoplastic cells, has been observed in carcinoma cells of the large intestine. The features of this pattern are high DPN diaphorase and TPN diaphorase activities and low succinic dehydrogenase, α-glycerophosphate dehydrogenase, and monoamine oxidase activities as demonstrated by the morphologic histochemical technics employed.[2] The distinctive histochemical reaction pattern found in carcinomas of the large bowel is not present in all cells of these lesions. It is most consistently observed in the cells of the invading tumor margin, in cells at the periphery of tumor cell aggregates, and in isolated cell groups; it is least common in areas of carcinoma which either do manifest or, because of location, are likely to manifest degenerative changes. The pattern occurs in a higher proportion of poorly differentiated carcinoma cells than of well-differentiated carcinoma cells. This distribution suggests that the distinctive enzyme pattern observed is characteristic of the more malignant cells of this type of neoplasm. Several types of reaction pattern are found in cells of benign adenomatous polyps, but all of them differ from the distinctive pattern found in carcinomas. In malignant polyps, the areas of carcinoma show the same distinctive reaction pattern as that found in manifestatively infiltrating carcinomas.

The application of morphologic histochemical technics to the study of disease processes is still in its infancy. With the passage of time one may expect detailed investigations of a wide variety of pathologic entities and a consequent better understanding of the basic biochemical changes occurring in disease. Likewise, these technics give promise of new and more sensitive diagnostic criteria and of the possibility of more rational and closer ties between therapy and its effects on the biochemical abnormalities which are the basis of so many disease processes.

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References: 1. Kanof, N. B., and Blau, S.: *New York J. Med.* 59:2184 (June 1) 1959.
2. Smith, J. G., Jr.; Zawissa, R. J., and Blank, H.: *A.M.A. Arch. Dermat.* 78:643 (Nov.) 1958.

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*TRADEMARK

Forensic Medicine

Traumatic Cyanosis: A Report of Two Cases

YOUSIF D. AL-NAAMAN*

Columbia University College of Physicians and Surgeons, New York

ON June 14, 1837, 23 persons were crushed to death in a skirmish which occurred at the Champ de Mars, Paris. In reporting their deaths, Ollivier[1] gave the first description of a syndrome which he called *masque ecchymotique* or traumatic asphyxia. In 1870 Tardieu[2] reported nine cases of this condition, and in 1946 Dwek[3] reviewed 170 cases. In 1951 Reichert and Martin[4] reported a case in which there was concomitant paraplegia, and Nyhus and Cook[5] described a case in 1953. However, the cases which have been reported in the literature do not exceed 200.

YOUSIF D. AL-NAAMAN

*Formerly Resident in Thoracic Surgery, Baylor University College of Medicine Affiliated Hospitals, Houston, Texas; presently Research Fellow in Cardiovascular Surgery, New York Heart Association and Columbia University College of Physicians and Surgeons, New York, New York.

Ecchymotic mask or traumatic cyanosis is a syndrome encountered after acute traumatic compression of the chest and upper part of the abdomen. The condition can be induced by pressure in panics accompanying fire, airplane crashes or other accidents. It also occurs to a lesser degree during physical exertion such as severe vomiting, difficult labor or whooping cough. Sudden doubling of the body in a jackknife injury or a rapidly growing dissecting or ruptured aneurysm of the aortic arch may produce the syndrome. It also has occurred during deep-sea diving and epileptic attacks.

The condition is characterized by cyanotic discoloration of the skin of the face, neck, upper part of the thorax, and the conjunctivae. The cyanosis is thought to be due to sympathetic vasomotor paralysis leading to distention and stasis of the capillaries rather than to true rupture and extravasation. The syndrome is caused by a sudden increase in pressure within the thorax and upper part of the abdo-

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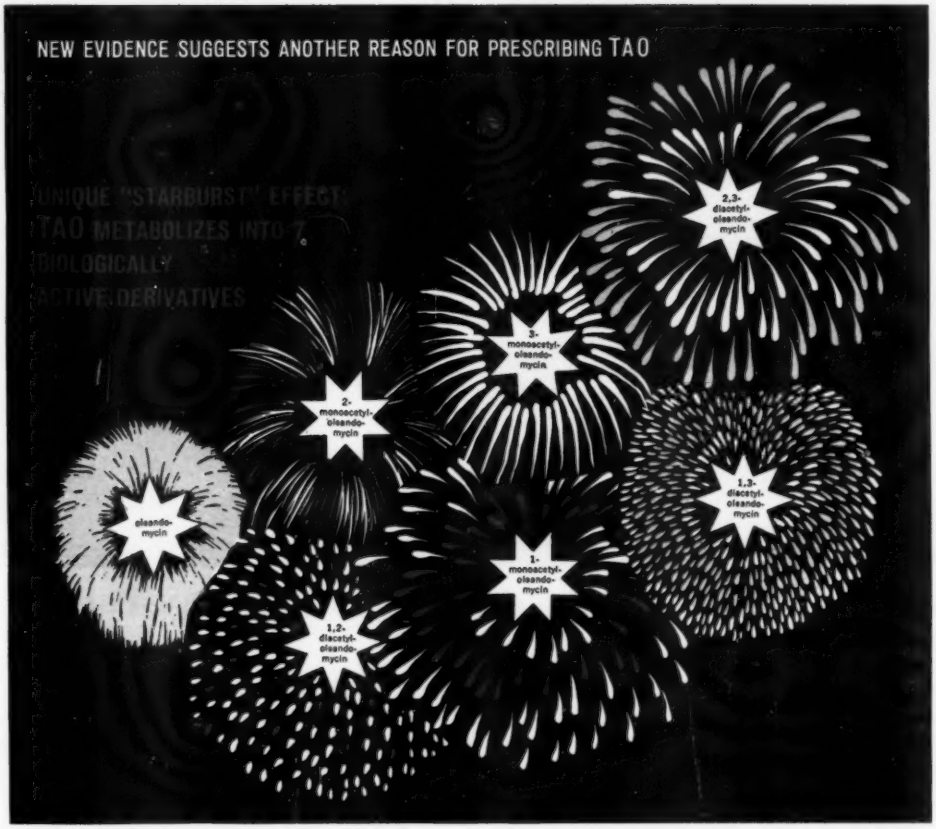

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FIGURE 1. Case 1. Cyanosis of the face, neck and upper part of the chest.

FIGURE 2. Case 2. Dusky discoloration and petechiae of the head, neck and upper part of the chest.

men, which lasts for two to three minutes and produces temporary cessation of respiration. Owing to the lack of valves in the superior vena cava and innominate veins and to the incompetence of the valves in the jugular veins, a reversal of blood flow occurs and causes rapid filling of the capillaries with vasomotor paralysis and stasis.

Case Reports

Case 1—A two year old boy was admitted to Jefferson Davis Hospital in Houston shortly after he fell from a slowly moving car onto a concrete driveway, striking his abdomen. His blood pressure was 90/50, pulse 160, temperature 103° F., and respiration 48. Cyanosis and petechial hemorrhages of the head and neck spreading to below the clavicle and prominent conjunctival hemorrhage were present (figure 1), and there were several episodes of vomiting. Associated injuries included fracture of the upper end of the ulna, dislocation of the head of the radius and a dislocation of the left shoulder.

Treatment included oxygen, bed rest, and reduction of the fracture and dislocations. Tachycardia persisted for several days and faded gradually, and there was gradual clearing of the cyanosis. The patient became afebrile on the third day and was discharged on the fifth day after admission.

Case 2—An 18 month old boy was run over by a slowly moving car and was thrown to the ground on his abdomen. The child did not breathe for about two minutes and then turned "red and spotty" and vomited three times. He was admitted to Jefferson Davis Hospital with dusky discoloration and petechiae of the head, neck, shoulders and upper part of the chest and conjunctival hemorrhage (figure 2). His blood pressure was 90/60, pulse 80, temperature 99.4° F. and respiration 28. He was treated symptomatically and was discharged on the twelfth day after admission.

Discussion

In both of the cases just described, there occurred acute compression of the thorax and upper part of the abdomen lasting for two to three minutes. The compression produced temporary occlusion of the superior vena cava

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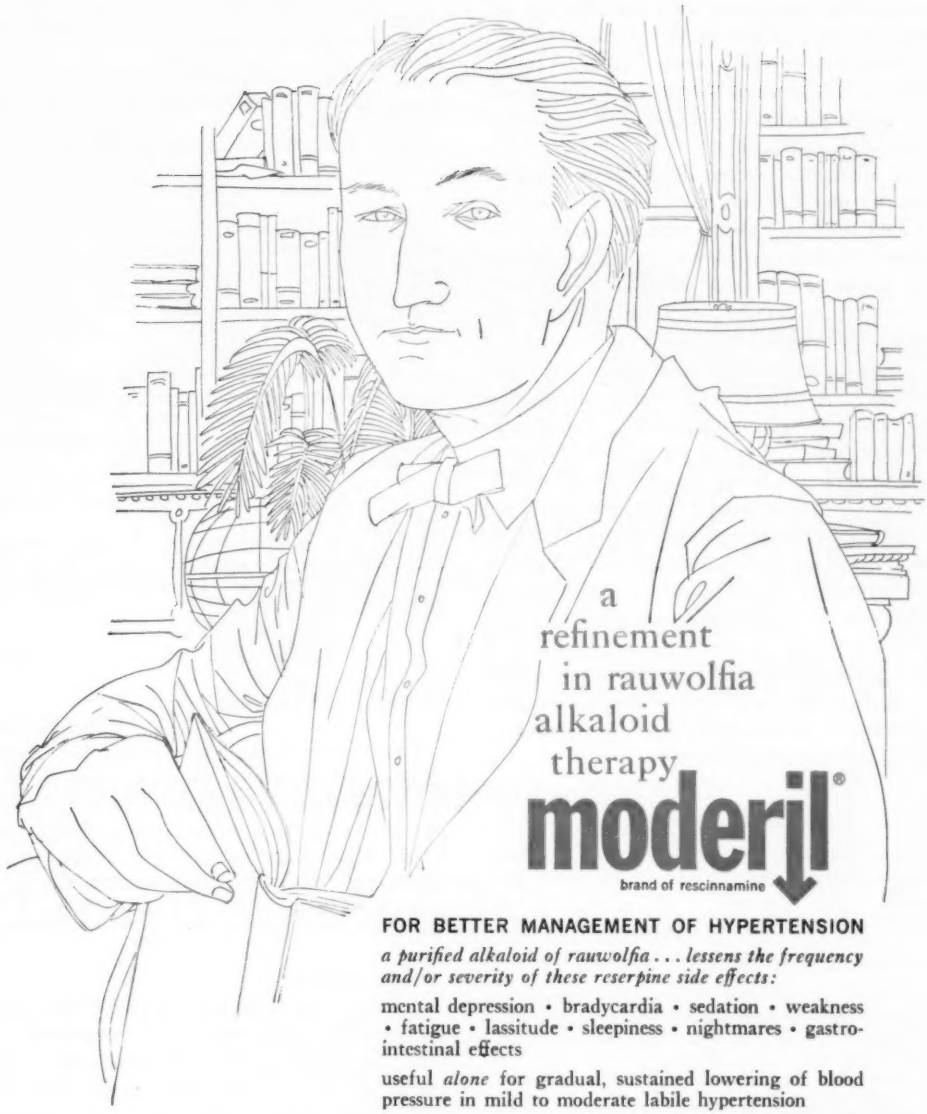

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and a sharp and sustained increase in venous pressure sufficient to reverse the flow of blood in the superior vena cava. Since there are no valves in the innominate vein and only incompetent, if any, valves in the jugular system, the blood was forcibly ejected in the reverse direction. This caused stasis of the apparently temporarily paralyzed venules and capillaries of the head and neck.

The syndrome, which does not necessarily follow trauma, may be mild or may be severe and lead to death. Death may result from associated injuries and their complications or from prolonged compression of the thorax with cessation of respiration for a period sufficient to cause cerebral anoxia.

The increased venous pressure in the jugular veins may also cause a carotid sinus reflex mechanism and subsequent death. Any condition which obstructs the superior vena cava, e.g., intrathoracic tumors, mediastinal emphysema and hematoma, will produce many of the findings of traumatic asphyxia, although the mechanism is not quite the same. However, this syndrome does not usually result from the penetration of high-velocity missiles into the thorax.

The prognosis is good if the trauma does not cause death shortly after its occurrence. Treatment is symptomatic and, if necessary, oxygen may be administered.

ACKNOWLEDGMENT

I wish to express my gratitude to Dr. M. E. DeBakey, my former professor, for allowing me to report these two cases.

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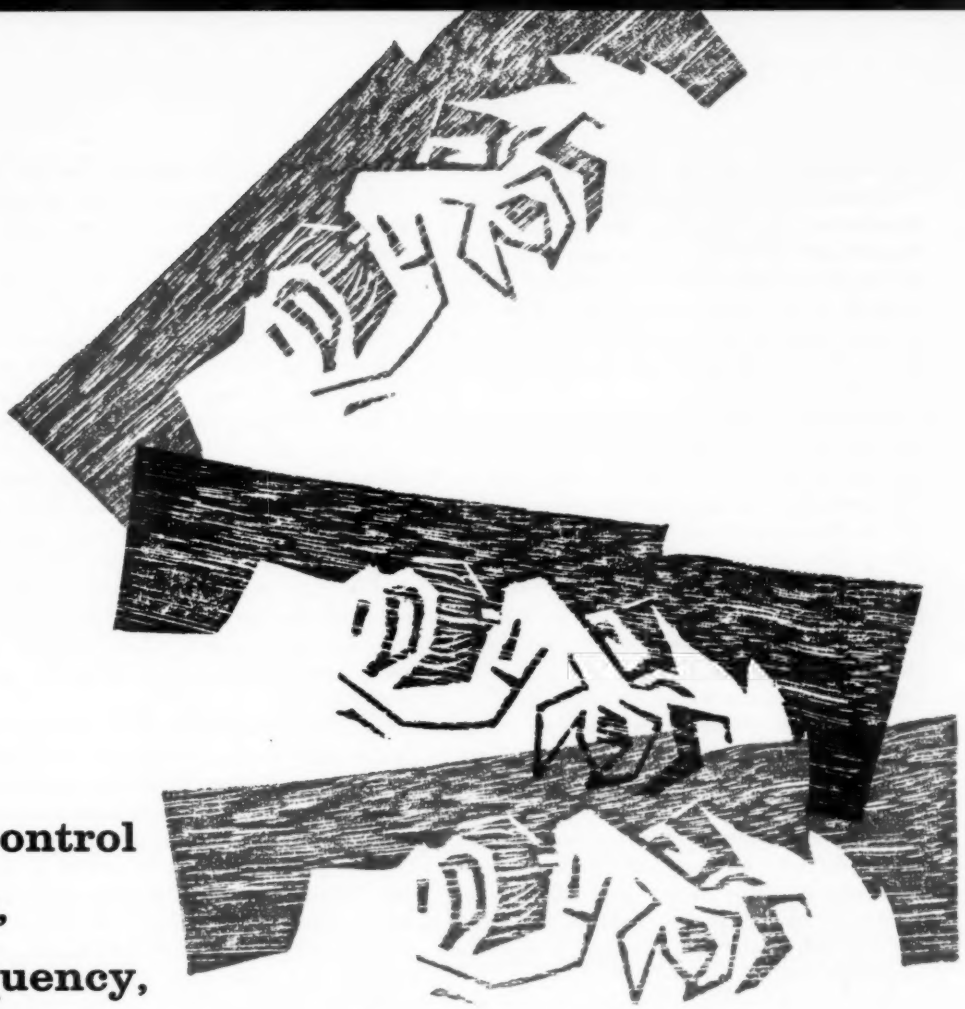
CORRESPONDENCE

The writer of the letter which follows has granted permission to publish his remarks which refer to the article, "The judge looks at the impartial doctor," by Justice Aron Steuer, published in the December issue of Postgraduate Medicine. *The letter also describes a program being studied and tested in Toledo, Ohio.*

To the Editor:

I have read with keen interest the recent article, "The judge looks at the impartial doctor."[1] In Toledo, a city of about 300,000 population, we have an Academy of Medicine-Bar Association Joint Committee that has been studying that problem as outlined in the book by Justice Peck and collaborators. We have felt that our community is sufficiently small not to require the "impartial expert," as most of the physicians are well enough known to

(Continued on page A-64)



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one another to act as a safeguard against "charlatanism," as you suggest. Similarly, the members of the committee felt that the court requires and is entitled to a reasonable evaluation of the degree of disability suffered by the plaintiff in his claim for disability but that we as physicians should not always be placed in an adversary attitude in order to arrive at that conclusion.

It is a fairly common practice in this area that the opposing attorneys exchange their respective medical reports on the case involved. Our committee has agreed to go a step farther and, on the authority of the opposing attorneys plus permission of the litigant, to allow the several medical examiners a conference or joint examination in order to agree, if possible, on diagnosis, prognosis and degree of disability. This is to be submitted as a final report to both attorneys and the court. Such an approval would eliminate the problems of the "impartial expert," as you point out so well, and should at the same time give as impartial a medical report to the court as is possible. Of course we realize the objections to be raised by the plaintiff's attorney but why must we as physicians be subjected to the battles of the courtroom when it has not been of our making? Our job is only that of trying to help sick people get well!

The legal profession frequently refers to the great differences which exist in the "schools of thought" in medical practice. I'm not so sure that such great differences exist basically, but that they are rather "prejudices" built up in the minds of the medical examiners who are so inclined or so influenced by the adversary attitude.

Should the law allow the composite testimony to be presented to the court without causing the medical examiners to be used as "pawns" by the respective attorneys to help win their side of the case, the medical profession might be less reluctant to testify in those personal injury cases into which we are forced by virtue of the subpoena and not by our own choosing, believe me! Of course we realize that the average layman is hailed into court because of his knowledge of a particular case; but his is usually a singular occurrence whereas ours recurs repeatedly—and increasingly so.

In light of these, and other arguments, our Joint Committee is launching a pilot study of a pretrial conference by the involved medical examiners, in the absence of legal talent. They will submit a final report to the legal parties. This we propose as a better method in presenting impartial medical findings—and from a strictly medical standpoint. Of course, where a difference of opinions is warranted, it will be duly included. Then let the lawyers take up the cudgel and battle out the question of liability and damage without having us physicians in the "middle." Thus, maybe we may eventually bring about better liaison between the medical and legal professions, and finally, we hope, better cooperation between these two fine bodies.

In closing, I wish to comment again on the excellence of Justice Steuer's article. If any reprints are available, would you kindly send me several to be used for study by our Joint Committee?

Yours very sincerely,

MAX T. SCHNITKER, M.D.
Member, Academy of Medicine-Bar Association Joint Committee, Toledo, Ohio

REFERENCE

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Roentgen Diagnosis of Lesions of the Esophagus, Part 2

JAMES R. WILLIAMS† AND PAUL C. HODGES

University of Chicago, Chicago

Perforation of the Esophagus

PERFORATION of the esophagus may result from endoscopy, dilatation of strictures, penetrating foreign bodies, or severe vomiting. Chest films show air in the mediastinum and in the soft tissues of the neck, sometimes with pneumothorax (figure 18).

Peptic Esophagitis

Peptic esophagitis is caused by the regurgitation of acid gastric content into the esophagus, common underlying factors being esophageal hiatus hernia or the persistent vomiting of stenosing duodenal ulcer. Surgical resection of the cardioesophageal junction permits regurgitation and frequently is followed by esophagitis, the complaints being substernal or subxiphoid burning on lying down and pain after swallowing. The x-ray findings are ulceration of the lower esophagus, followed eventually by a smoothly tapering stricture just above the level of the diaphragm (figure 19). When ulceration is not visible and the stricture is not completely smooth, differentiation from carcinoma is difficult.

Neoplasms

Squamous cell carcinoma may occur at any level of the esophagus but is most frequent in the middle third. The usual complaint is difficulty in swallowing solid foods with a sensation that the food is lodging somewhere in the chest. In x-ray films, the lesion appears as an irregular intraluminal mass with abrupt transition from normal to abnormal mucosa, particularly at the upper margin (figure 20). The lesion frequently encircles the esophagus completely, producing an irregular narrowing with varying degrees of obstruction. Usually it appears to extend longitudinally for only a few centimeters, but histologic examination al-

*Emeritus Professor and Chairman; †Assistant Professor; Department of Radiology, University of Chicago, Chicago, Illinois.

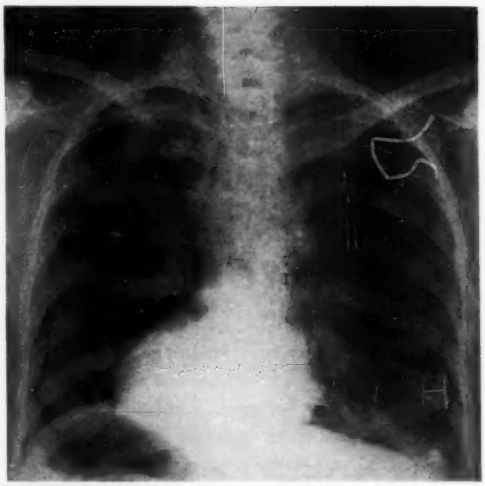
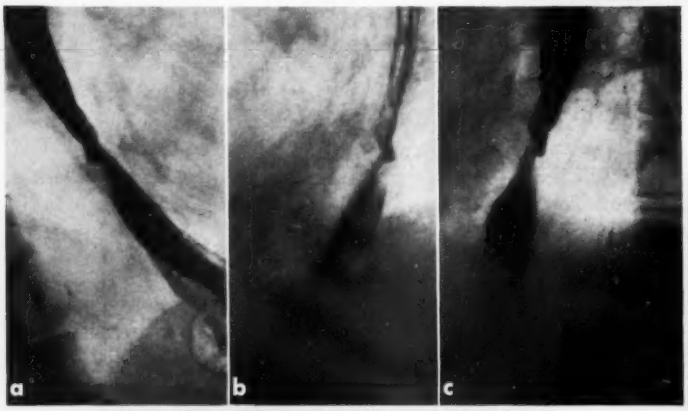


FIGURE 18. Perforation of esophagus during instrumentation. Air has leaked from the esophagus into the mediastinum, the right pleural cavity, and the subcutaneous tissues of the pectoral region and the neck.

FIGURE 19. Peptic esophagitis. Reflux of acid gastric content has produced an ulcer crater which is seen in all three views. The concentric hiatus hernia, presumably responsible for the reflux, shows in (c).



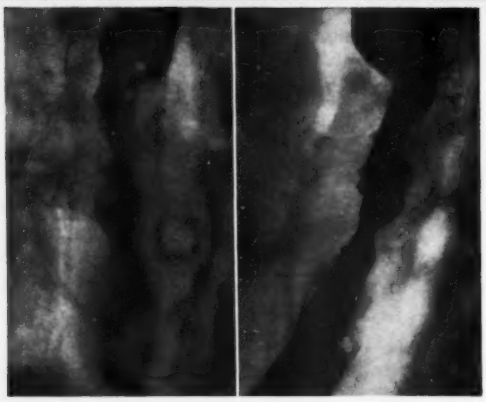


FIGURE 20. Squamous cell carcinoma of esophagus—an extensive lesion involving the entire middle third of the esophagus with multiple irregular, polypoid, intraluminal masses.

FIGURE 21. Squamous cell carcinoma of esophagus. In this case a small annular carcinoma was present at the junction of the distal and middle thirds of the esophagus with a secondary squamous cell carcinoma at the diaphragmatic end.

FIGURE 22. Adenocarcinoma of lower end of esophagus and adjacent gastric cardia.

ways shows greater longitudinal extension than is suggested by radiology. Spread of the neoplasm through the lymphatics may produce two masses in the esophagus, which are separated by a considerable segment of normal mucosa (figure 21).

Adenocarcinomas of the esophagus rarely occur above the lower third. Whether they result invariably from extension of a carcinoma of the cardia of the stomach or whether sometimes they may arise from rests of gastric mucosa in the lower esophagus is of little practical importance, because when the patient comes to see the radiologist the stomach usually is involved. Those carcinomas which produce polypoid masses in the distal esophagus

FIGURE 23. Carcinoma of lower end of esophagus and gastric fundus, simulating cardiospasm.

FIGURE 24. Metastatic carcinoma of the esophagus. Metastases from carcinoma of breast, developing 12 years after radical mastectomy, were proved by biopsy and subsequent autopsy.

FIGURE 25. Corkscrew esophagus. A spectacular but symptomless and apparently nonsignificant variant of the normal esophagus. Note the phrenic ampulla below.

FIGURE 26. *Left.* Achalasia (cardiospasm). The esophagus, dilated above, tapers down to a string below. At fluoroscopy, the diameter of the narrowed segment could be seen to fluctuate with respiratory phases.

FIGURE 27. *Right.* Scleroderma. Cutaneous scleroderma for 15 years, dysphagia for eight years. Esophagus is rigid, devoid of peristaltic activity, and unable to squeeze itself dry after food has passed. In this view most of the barium has passed into the stomach and the rigid esophagus above has filled with air from the pharynx.

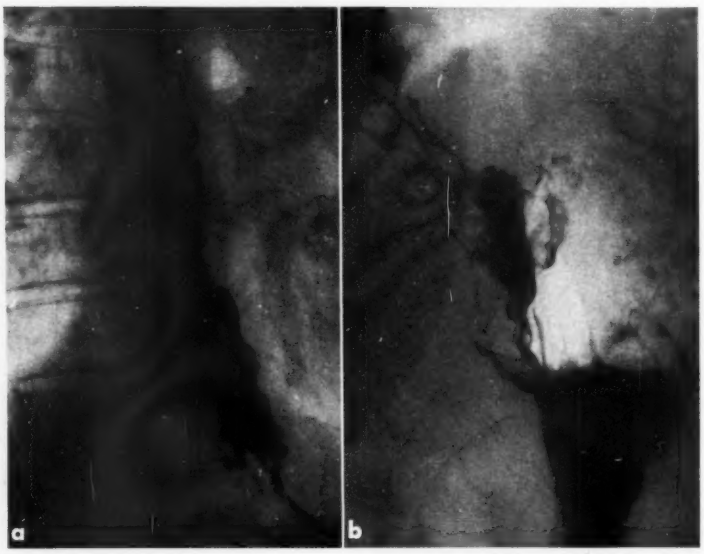


FIGURE 28. Esophageal varices.

a. The wormlike intraluminal masses of distended blood vessels stand out as negative shadows contrasted with barium in the esophagus.

b. The varices extend into the gastric fundus.

and fundus are easy to recognize (figure 22), but the unaided x-ray examination cannot distinguish from cardiospasm or peptic esophagitis those neoplasms which produce relatively smooth narrowing of the lower esophagus (figure 23).

Benign neoplasms of the esophagus are rare, but neurofibromas and leiomyomas have been reported. The x-ray appearance is that of a smoothly rounded submucosal mass underlying intact esophageal mucosa. The esophagus may be invaded by direct spread from a contiguous bronchogenic carcinoma, and mediastinal metastases from a distant primary, particularly carcinoma of the breast, may invade the esophagus (figure 24).

Abnormalities of Motility

The normal contraction wave of the esophagus, which is a continuation of the deglutition

contraction of the pharynx, proceeds slowly down the esophagus to the diaphragm, pushing the swallowed bolus before it and leaving an almost clean esophagus behind. In older subjects and in the presence of a partially obstructing lesion of the lower esophagus, multiple irregular, ineffective, nonprogressing contraction waves may appear. These contractions produce several dilated segments separated by contracted segments and should not be mistaken for multiple diverticula. Sometimes such contractions produce a spiral "corkscrew" configuration to the lower esophagus (figure 25).

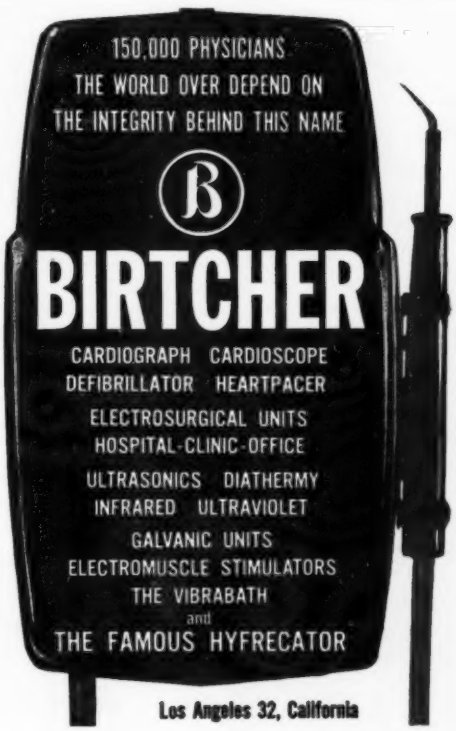
Achalasia of the esophagus (cardiospasm) is a failure of the terminal portion to relax and thus permit emptying into the stomach. As a result swallowed food is retained and the esophagus dilates. The underlying mechanism may be neurogenic, similar to that in Hirschsprung's disease of the colon (congenital megacolon), in that the terminal segment of the esophagus fails to relax or there is failure of propagation of the normal contraction wave. One sees a long, tapering, narrowed lower segment and a dilated, elongated, tortuous proximal segment (figure 26). Multiple ineffective, nonprogressing contraction waves are visible fluoroscopically in the dilated segment and this dilated portion usually contains air and particles of food. Emptying of the esophagus into the stomach occurs in spurts, usually on expiration.

Scleroderma

Patients with scleroderma frequently experience difficulty in swallowing, particularly when they are lying down, and occasionally this symptom precedes the development of characteristic skin lesions. Fibrosis occurs in the submucosa and muscularis and, as a result of this, the esophagus changes from an extremely flexible, distensible, collapsible organ into a dilated and relatively rigid tube. Fluoroscopically one sees marked diminution or absence of contraction waves and when the patient is in the recumbent position, the esophagus retains barium almost indefinitely. When the patient stands, the barium flows slowly into the stomach, following which the rigid, slightly distended esophagus fills with air. The distention of scleroderma is moderate, however, compared with that sometimes seen in cardiospasm (figure 27). Scleroderma of the esophagus may be complicated by a superimposed peptic esophagitis, a condition which produces an area of constriction in the distal pharynx.

Varices

In portal hypertension, the shunting of blood from the portal circulation to the systemic venous circulation frequently leads to the development of varices in the esophagus and stomach. Radiologically, these appear as irregular, tortuous, wormlike intraluminal masses seen best when the esophageal mucosa is lightly coated with barium (figure 28), and similar varices may be seen in the gastric fundus. Esophageal and gastric varices may be demonstrated directly by the so-called splenoportal venography in which serial upper abdominal films are made following injection of an aqueous solution of an organic iodine compound into the spleen.



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References: 1. Bickerman, H. A.: in Drugs of Choice, Mosby, St. Louis, 1958, p. 557. 2. Lhotka, F. M.: Illinois M. J. *112*:259 (Dec.) 1957. 3. Fabricant, N. D.: E.E.N.T. Monthly *37*:460 (July) 1958. 4. Farmer, D. F.: Clin. Med. *5*:1183 (Sept.) 1958.

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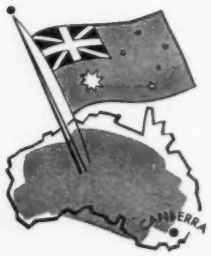

Malignant melanoma—Dr. R. I. Mitchell of the Royal North Shore Hospital of Sydney reviewed all cases of malignant melanoma of the skin and mucosa treated at this hospital from January 1951 to December 1954. Of the 53 patients in this series, 21 have survived. There were 21 men and 32 women, and the patients affected most frequently were those 41 to 50 years old, with another peak occurring in the age range of 71 to 80 years. Lymph node metastases developed in 19 patients at some stage of the disease and, although no record is available, it is probable that this complication occurred in the other patients. Four years after operation 19 patients were alive and apparently free of disease, two were alive but were known to have active disease, 24 had died, and eight could not be traced.

In discussing this disease, Dr. Mitchell stated that the majority of malignant melanomas originate from pre-existing moles. The pigmented nevus is the most common of all skin tumors, with an average of 15 moles for every adult white person. All nevi probably are congenital, but they may not appear until later in postnatal life. The hormonal stimuli of puberty and pregnancy are known to cause the sudden appearance of numerous dark moles previously unnoticed or inconspicuous, and these stimuli commonly cause pre-existing moles to enlarge and darken.

Malignant melanomas never arise from intradermal nevi; about 90 per cent of them occur in junctional nevi. Only a small proportion (about 10 per cent) of melanomas arise in compound nevi, which contain dermal and junctional elements and clinically resemble dermal nevi. It is because of this small proportion that any common mole showing activity should be excised. Blue nevi (Jadassohn) are composed of spindle-shaped melanoblasts deep in the dermis. They are benign tumors and can exist for many years without change; it is only rarely that a blue nevus may give rise to a malignant melanoma.

Visceral metastases occur quite commonly and are found most frequently in the lungs and liver. Melanosis coli is not related to the metastasis of malignant melanoma, but is a pigmentation of the mucosa of the colon and rectum resulting from the habitual use of purgatives containing phenolphthalein.

Whenever possible, the principle of en bloc excision of the primary tumor in continuity with the draining lymph nodes should be followed because of the high incidence of lymphatic metastases. Whether or not this is practicable depends on the site of the primary tumor. The method formerly advocated of excising a strip of fascia and skin from the primary tumor to the lymph nodes is unsound. If the primary tumor is so situated that dissection of the lymph nodes in continuity is not practicable, such as lesions distal

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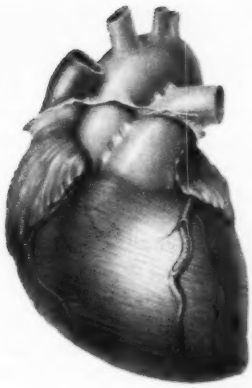
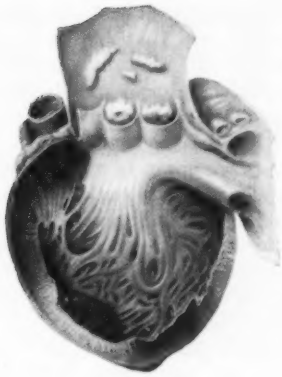


IN ANGINA PECTORIS AND CORONARY INSUFFICIENCY

. . . the treatment must go further than vasodilation alone. It should also control the patient's ever-present anxiety about his condition, since anxiety itself may bring on further attacks.



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to the knees or elbows, then prophylactic dissection of the clinically nonaffected nodes is not recommended. These nodes may act as filters if left *in situ*; also, the lymphedema and lymph stasis which follow prophylactic dissection lead to imprisonment of any free melanoma cells in the limb, and they then appear as multiple subcutaneous deposits along the lymphatics. If the draining lymph nodes appear to be clinically involved, radical dissection is the treatment of choice regardless of the site of the primary tumor. Such dissection may be continuous or not, depending on the location of the melanoma.

Alcohol in body fluids—The rise of alcohol concentration in the blood after drinking was studied by Drs. R. C. Bayly and N. E. W. McCallum of the Laboratory of Forensic Science at the University of Melbourne. Their series included 56 men who had consumed beer at their fastest rate on an empty stomach. The increase in alcohol concentration ranged from 0.003 to 0.083 per cent, with an average of 0.039 per cent; it exceeded 0.05 per cent in 14 patients (25 per cent). When the rate of drinking was varied, there was usually a significant increase if the period of rapid drinking occurred in the final stages. The time taken for attaining the maximal alcohol concentration in the blood was reduced by increasing the concentration of the beverage, but this was the only clear-cut result obtained. The presence of food in the stomach before drinking lowered the maximal concentration attained under otherwise identical conditions, while the rise in concentration after drinking and the length of time required to attain maximal concentration were reduced in most of the patients. It was concluded from this study that an accurate assessment of alcohol concentration in the blood cannot be made before a blood sample is taken.

These reports appeared in the *Medical Journal of Australia.*

AUSTRIA

Atresia of the ileum—The first successful operation without resection for atresia of the ileum was performed by Fockens in 1911, and Demmer was credited with the first successful surgical procedure with resection in 1921. However, the literature contains very few reports of successful operations for this condition. Because of this fact, F. Helmer demonstrated such a case to the scientific meeting of the Vienna Society of Physicians.

The patient presented was a seven month old, normally developed boy who had had two operations for atresia of the midportion of the ileum. The first operation was performed when he was two days old; the second was done 10 days later. At the first surgical intervention, a double-channel ileostomy of extension was prepared; at the second operation, this was resected and an end-to-end anastomosis was done with two layers of atraumatic interrupted (single-knot) sutures. This method, recommended by Gross, was found to be satisfactory.

In discussing this case, H. Kunz said that in adult patients a two stage resection of the small intestine usually is not successful. However, in the presence of a large incongruity of the intestinal lumens in newborns, operative risk is much less if the surgical procedure is done in two stages.

R. Jonas reported that in operating on a child with this condition he had not performed a surgical closure of the ileal fistula. Eight weeks after the operation, the fistula was essentially smaller and indications were that it would close spontaneously in a short time.

H. Hajek pointed out that a problem to be considered in such cases involved the influence of the intestinal contents on the development of the wall. He also asked how the peristaltic wave mechanism functioned in the intestinal segment located aborally from the site of the atresia. Helmer replied that at the time of the operation the passage of the aboral intestinal segment must be tested, since multiple atresias may be present. Sodium chloride solution is injected from the direction of the aborally situated blind pouch; this produces peristaltic waves which bring the fluid down as far as the rectum. In the case which he presented, washings were passed on the sixth postoperative day. After the anastomosis was prepared, the intestinal function soon became normal. Following the second operation, evacuation of the intestine was normal but occurred frequently for awhile.

Helmer also pointed out that severe nutritional disturbances usually accompany resection for ileum atresia and that complete recovery from this operation may not be effected for as long as three months.

(Continued on page A-94)

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BRAZIL

Gastric biopsy—In a study of gastritis by J. de S. Meireles, M. R. Montenegro, H. Espejo and J. F. Pontes, gastric biopsy was performed on 58 patients, using either the Australian tube or the Tomenius tube. Specimens were obtained easily with the former instrument, but it was impossible to control the aim when the Tomenius tube was used.

The specimens were studied histologically and classified according to the criteria of Herning. The important elements in the diagnosis of atrophic and superficial gastritis, as well as the appearance of normal gastric mucosa, were evaluated by microscopic analysis. The histologic findings were plotted against clinical data.

The following conclusions were made:

1. By using the Australian tube under roentgenographic visualization, biopsies were performed easily and yielded good specimens for histologic study.

2. Gastric biopsy is very useful in the study of gastritis, but is worthless in cases of localized gastric disease.

3. Intestinal metaplasia and dissociation of the muscularis mucosae were found only in atrophic gastritis.

4. Gastric mucosa can be considered normal in the absence of alterations in the ostium and foveola of the gastric glands.

5. Mild inflammatory cell infiltration and a low degree of glandular cell degeneration are found even in normal gastric mucosa.

6. There was no histologic evidence of atrophic gastritis in one case of histamine achlorhydria.

This report was abstracted from *Revista do Hospital das clínicas da Faculdade de medicina da Universidade de São Paulo.*

Toxicity of chlorinated and organophosphorus insecticides—In *Revista paulista de medicina*, W. F. de Almeida reported on the symptomatology and treatment of cases of toxicity due to several chlorinated and organophosphorus insecticides. He stressed the use of preventive measures for those persons who work with these preparations.

The large-scale agricultural application of the modern insecticides, used first in cotton fields and then in truck farming crops and orchards, has definitely increased the human toxicity problem. Because many of these agents are easily absorbed percutaneously, they are highly toxic to humans.

Insecticide intoxication cases in São Paulo are caused chiefly by PARATHION® and METASYSTOX®.

South American blastomycosis—T. A. Furtado, C. F. Lopes, N. de Almeida, Jr., J. A. Moreira and L. G. Pimenta discussed six patients with this disease in *O Hospital.* In four of these patients, the blastomycosis was resistant to sulfonamides. All patients were treated with 50 mg. amphotericin B suspended in 500 cc. of 5 per cent dextrose in water and administered intravenously by the drip method over a period of six to eight hours. Total dosage ranged from 955 to 1600 mg.

The results were good in three cases, fair in two, and poor in one. Although amphotericin B has a therapeutic effect on South American blastomycosis and may be valuable in treating sulfonamide-resistant disease, its total efficacy must be determined by observing a large number of patients with a long follow-up evaluation.

Premenstrual tension—This syndrome, including general considerations and an analysis of the symptomatology, etiopathogenesis and therapy, was discussed by J. R. Azevedo in *Revista paulista de medicina.* Following treatment with a single preparation containing chlormerodrin, meprobamate and vitamins A and E, 80 per cent of the patients with premenstrual tension were completely "cured."

Antigen in Chagas' disease—A new antigen for the complement-fixation test in Chagas' disease was described by S. M. Batista and U. M. Santos in *O Hospital.* The antigen is extracted with methyl alcohol (after being treated with acetone) from the lyophilized powder of *Trypanosoma cruzi.* It is easy to prepare, may be kept at room temperature with no change in titer for at least two years, and shows greater specificity and almost no anticomplementary action.

The antigen was tested with excellent results in 310 samples of serum from 98 patients with Chagas' disease with positive xenodiagnosis, 42 with syphilis, 30 with pulmonary tuberculosis, 12 with cutaneous leishmaniasis, 12 with kala-azar, 36 with leprosy, 50 with *Schistosoma mansoni*, and two with pemphigus foliaceus. In the control group were 369 school children and Indians whose serum was negative.

(Continued on page A-96)

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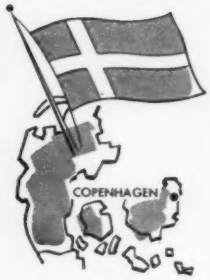


Effect of Lisidonil on bladder dysfunction—Twenty-eight patients with multiple sclerosis were observed to discover the effect of Lisidonil on bladder dysfunction. Palle Juul-Jensen and Ejner Pedersen showed that the drug is effective in patients with a cystometrogram of the "uninhibited neurogenic" type, which is evidenced clinically by frequent and urgent micturition. In many of the patients, micturition approached normal during the treatment. In the patients with functional "reflex neurogenic bladder," the treatment resulted in longer intervals between urinations. In routine treatment, the initial dose of Lisidonil should not be higher than 5 to 10 mg. per kilogram of body weight every 24 hours.

Intraspinal hydrocortisone treatment—The spinal fluid in man contains hydrocortisone (compound F) in concentrations from 1.2 to 7 μg. per 100 ml., corresponding to about 20 per cent of the blood values. Because of the blood-liquor barrier, therapeutically active concentrations in the intraspinal space cannot be obtained by peroral or parenteral treatment.

In studying the problems involved in this treatment, Erik Skinhøj and Ole Buus found that intraspinal injection of hydrocortisone acetate apparently does not involve any risks. Depositing 100 mg. of hydrocortisone acetate by lumbar puncture provides a therapeutically active concentration in the spinal fluid which lasts at least three weeks.

Routine diagnosis of enteric viruses using tissue culture technics—Specimens for tissue culture were obtained from patients admitted to the hospital with a diagnosis of paralytic or aparalytic poliomyelitis or lymphocytic choriomeningitis.

From 106 patients with a clinical diagnosis of paralytic poliomyelitis 78 poliomyelitic strains were recovered. These consisted of 44 type I, 2 type II and 32 type III.

From 1,344 patients with an initial diagnosis of aparalytic poliomyelitis or lymphocytic choriomeningitis, only 264 (19 per cent) were found to excrete enteric viruses. More than half of the strains isolated (159) belonged to the ECHO 9 group of viruses. Only 27 patients were found to be infected with poliomyelitis virus. A variety of types of Coxsackie, adenoviruses and ECHO viruses accounted for 34 strains, while 51 agents were not identified.

Sixty per cent of the isolated ECHO 9 strains were found to be pathogenic for newborn mice after passage in tissue culture. Three ECHO 9 strains were found to be pathogenic for newborn mice without previous passage in tissue culture. Annelise Godtfredsen and Herdis von Magnis, who made these investigations, also found a difference in antigenic structure between the prototype ECHO 9 strain and a Danish ECHO 9 strain.

Protamine zinc insulin in crystalline suspension—C. Krayenbüll and J. E. Poulsen described a new protamine zinc insulin preparation as a primarily crystalline suspension. It is buffered with phosphate buffer and has the content of protamine, zinc and other components within the limits of the old primarily amorphous PZI. This new crystalline suspension has crystals of uniform shape, which do not change during storage under usual conditions.

Unlike the old amorphous preparation, the new crystalline suspension will bind only a small part of unmodified insulin if such insulin is added to the solution.

The clinical effect on the blood sugar is identical for the new and the old PZI. The new preparation, however, can be mixed in the syringe both with regular (unmodified) insulin or neutral protamine Hagedorn insulin (NPH) or both, without any noticeable change in the characteristic timing of the effect of the components of such mixtures on the blood sugar.

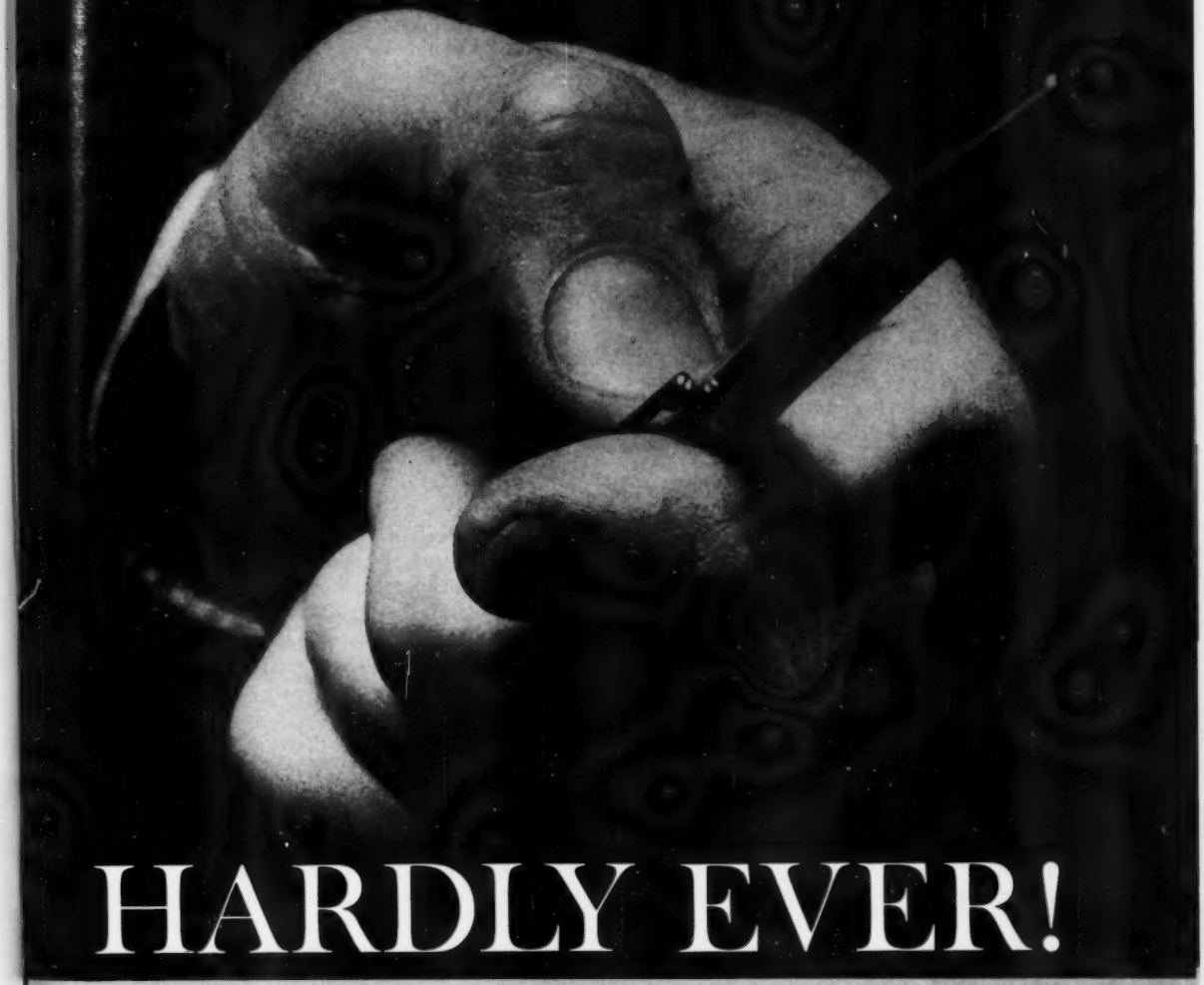
ENGLAND

Wound healing—Wound healing is a commonplace phenomenon, and like all commonplaces in medicine it requires critical review from time to time. Biologically it is as intricate and insoluble as the problem of growth itself; yet surgeons stitch up the abdomen by a method that has for each of them become a habit, and leave the rest to nature.

In an address on this subject at the Royal

(Continued on page A-98)

recurring infections? systemic reactions?



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WARNER CHILCOTT

MORRIS PLAINS, N.J.

Society of Medicine, Mr. Alan H. Hunt, surgeon to St. Bartholomew's Hospital, said that wound healing has been divided into three phases: (1) traumatic inflammation, including the period of cleaning up by phagocytosis, (2) the lag period, and then (3) the collagen phase. Yet it is all one vital process which begins at the moment the wound is inflicted. The great men of surgery, Halsted, Moynihan and Whipple, to mention but three, have all stressed what is now widely recognized—that incisions and dissections should be made with creation of as little dead tissue and with use of as little ligature material as possible, leaving the least amount of material to be removed by phagocytosis. It is easy to recognize that sloughs, foreign bodies, clots and infection delay the orderly progress of healing, but are there any methods in common use that should be critically examined?

The plastic surgeons have taught how to handle skin wounds—hemostasis of individual bleeding points and exact, full-thickness closure without compression or tension. They have made a precise study of the subject in that part of the body that can be seen by the most exacting of critics, the patient. The methods practiced on the surface, where appearance is all-important, should be applied in principle to the depths, where looks may not matter but where results may mean life or death, such as whether an anastomosis unites satisfactorily or leaks. For this reason Mr. Hunt said that he would like to see the all-layers, continuous "hemostatic" suture go out of use. Much slough may sometimes be seen at anastomoses after its use. More trouble should be taken to secure the bleeding points and to construct the anastomosis layer by layer. Nonabsorbable sutures should be interrupted and should not, as a rule, impinge on the innermost mucosal layer.

Diathermy is constantly criticized as a source of dead material. These criticisms are justified only if diathermy is not properly and lightly used—either to divide fascial planes, muscle or vascular adhesions or to coagulate individual minor bleeding points. To do minimal damage and achieve its purpose more rapidly than by clamp and tie, it must be used with precision. The finest toothless forceps are necessary for coagulating individual vessels.

Treatment of severe chronic asthma—Cortisone and corticotropin are known to be valuable in treating status asthmaticus, but opinions differ as to their use in chronic asthma. Good results have been reported with prolonged treatment, but the Medical Research Council reported in 1956 that the initial improvement in patients having cortisone, as compared with control patients, was not maintained.

Drs. David Phear, Keith Ball and Francis Page at the Central Middlesex Hospital, London, carried out a prolonged trial with steroids for a mean period of two to seven years in a group of 50 patients with severe chronic asthma. They have recently published their findings in the *Lancet*. These findings are at variance with those of the Medical Research Council, for these three physicians consider, as a result of their experience, that cortisone and corticotropin are of real value in severe chronic asthma.

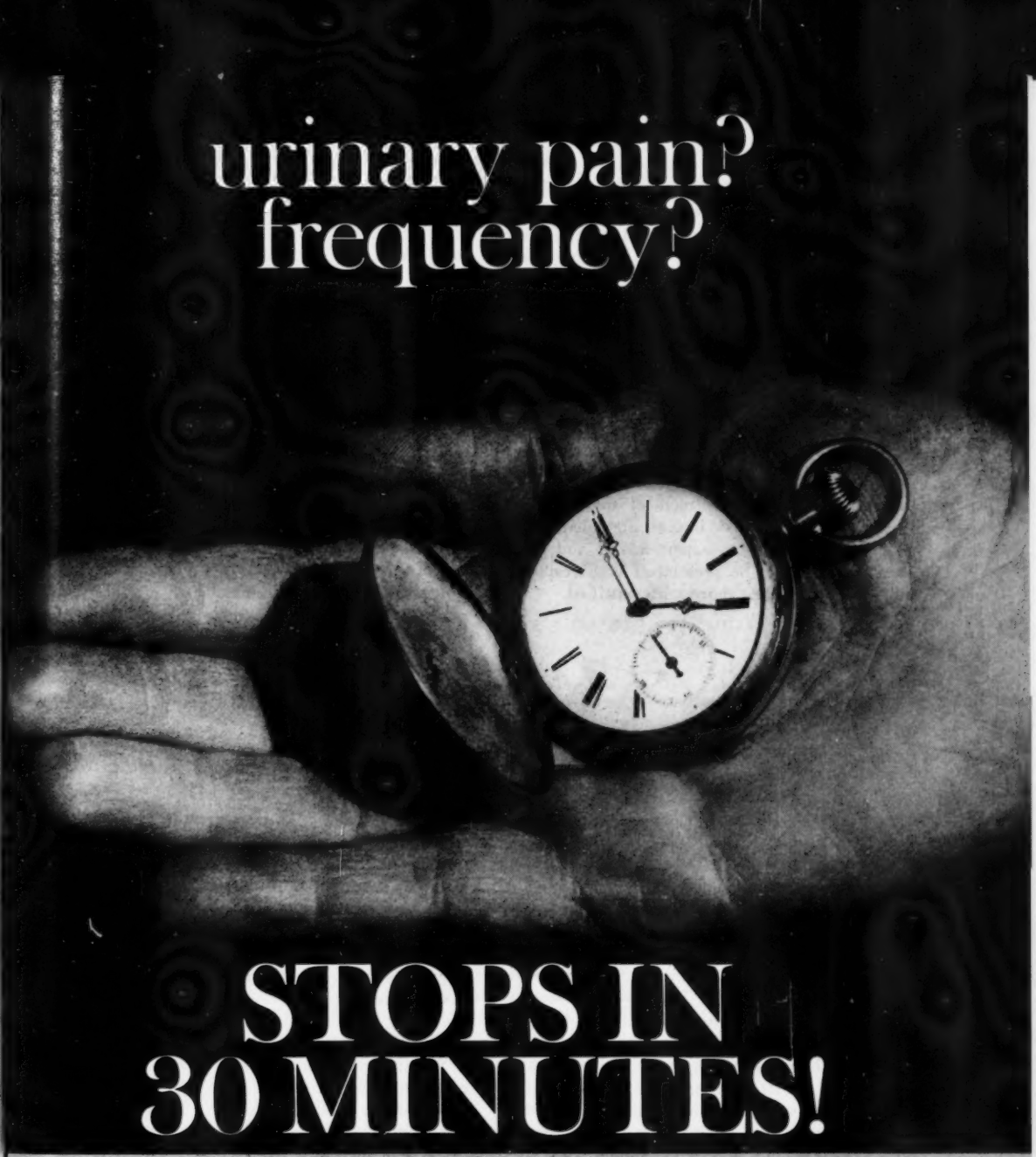
There were 33 women and 17 men in the group, 23 to 66 years old. All had severe chronic asthma which was resistant to conventional treatment and responded initially to steroids. Most of the patients had been unable to work or do their household duties for many months, and frequent hospital admissions had been necessary. Cortisone was given by mouth to 30 patients, most of whom needed 50 to 75 mg. daily. Corticotropin proved more effective in four cases, and 16 of the later cases were treated with prednisone. Response to treatment was assessed by the frequency of paroxysmal dyspnea, the capacity for exercise and work, and the degree of bronchospasm.

Good results were obtained in 39 of the 50 patients, and there was moderate improvement in five others. The results were poor in two women and one man with infective asthma, and three patients died during treatment. Twenty-one patients who were previously unable to work resumed their paid jobs or household duties. Apart from two cases of depression, side effects were slight.

Sleep without drugs—After a group of 14 articles by leading authorities on sedatives, tranquilizers and analgesics in the January issue of *Practitioner* came a refreshing antidote in the form of an article entitled "Sleep without drugs" by Dr. Hugh Barber of Derby, an esteemed and experienced physician. "Sleep without drugs," he wrote, "is natural and is common to the majority of human beings. It should be a matter of course in the young. There are no events in adolescence or young adulthood which justify the use of a sedative drug by way of preparation. To develop the right character with self-control and, if possible, with a sense of humor will make for restful nights."

(Continued on page A-100)

urinary pain? frequency?



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WARNER CHILCOTT
MORRIS PLAINS, N.J.

PY-GP02

As life's responsibilities increase, becoming less personal and with anxiety for others, there may be a tendency toward less peaceful sleep, but drugs should be avoided. People should be discouraged from calling a little lack of sleep by so high-sounding a name as insomnia. A generation or two ago many people dosed themselves as a matter of routine with some aperient. Perhaps today there is more risk in self-medication with sedatives. Patients in hospital receive hypnotics frequently. These should be discontinued for people at home, when recovery is probable.

Sedatives, tranquilizers and analgesics constitute a valuable part of medical treatment, in which much new work has accumulated. They should be studied with expert advice and guidance. They should be prescribed with responsibility and only when thoroughly justified.

FRANCE

Marks of premature old age—Dr. E. Aubertin, in the *Bulletin de l'Académie nationale de médecine*, stated that a number of general disturbances occur in people 40 to 60 years old whose chief complaint is tiredness. These disturbances are independent from the common diseases; they have nothing to do with gout, lithiasis, obesity, atherosclerosis, arterial ailments of the coronary vessels or of the limbs, or any disease which may be evolving. These people become less active; they begin to avoid sports, and they like to rest. They can no longer stay awake at night. Their movements are less quick, and their minds do not function promptly. They cannot recall proper names or telephone numbers. They are easily irritated and, as a consequence, they eat more and thus gain weight. They become breathless, their ears buzz, and noise bothers them. They doze after meals and sleep less during the night. Their sexual activity is diminished, and they have pain in the joints.

Clinical examination reveals only a slight elevation (about 90 mm. Hg) in the diastolic arterial pressure, some disease of the vertebral joints, and a slight increase in weight. Fundic tests of the eyes and an electrocardiogram give normal results. Biologic examination reveals a slightly higher level of nitrogen in the blood, a blood cholesterol value of about 250 mg. with 7 gm. of fat, and a higher level of beta proteins and blood sugar. Other symptoms include a higher level of alpha$_2$-euglobulins, increased blood viscosity, slowing of circulation, increase in blood potassium, and increased capacity for dissolving cholesterol.

Such persons are in the first stage of one of the metabolic diseases which attend old age, such as diabetes or atherosclerosis, but this stage is still reversible. Treatment is limited to practical hygienic procedures. Any stress and sexual excesses must be avoided, and caloric intake of lipids and, particularly, carbohydrates must be reduced. Use of tobacco and alcohol should be restricted. Only those medicaments which will not produce fermentation or intestinal putrefaction and constipation should be given; these include cholagogues of the artichoke type and liver extracts. Heparin may be given intravenously in small doses and at well-spaced intervals; pyridoxine and the citrate of betaine and choline also may be used. Deltacortisone may be given in short courses.

Epidemiology of tuberculosis—A number of articles on the epidemiology of tuberculosis have been published in the medical press as well as in the lay press with the intention of alarming the general public. Although it is true that the number of tuberculous persons has been greatly reduced, the number of people with chronic tuberculosis has increased. This results from incomplete cure with prolonged survival; such patients are carriers of the disease and are thus responsible for increasing the number of primary infections. The official statistics, however, are much less pessimistic, according to a report by Dr. Gabriel Roche in *Concours médical*.

Social security statistics from the French Social Insurance records listed 55,000 cases of tuberculosis in 1950 and 85,000 in 1956. However, the number of insured people and the consultations have increased. New cases detected at the dispensaries have decreased from 37,000 to 29,000. Routine compulsory examinations also revealed a reduction in tuberculous patients, from two to one per thousand among railroad employees and from seven per thousand in 1950 to 2.5 per thousand in 1958 among students. The statistics are difficult to interpret because of certain factors, such as the inclusion of cases of tuberculosis discovered before the system of obligatory examinations was introduced.

(Continued on page A-102)

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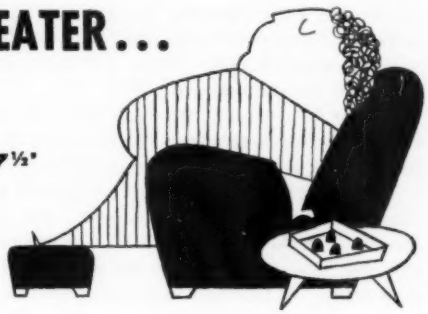

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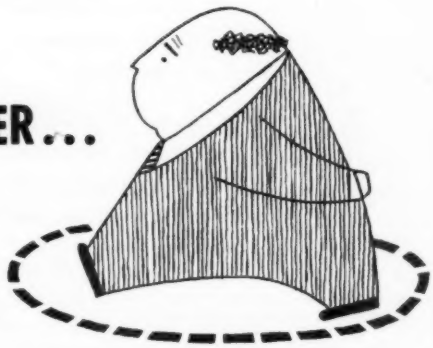

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STRASENBURGH

Of every 100 patients with pulmonary tuberculosis in 1930, 30 died, 50 were cured, and 20 had chronic disease. Since antibiotics have become widely used, 75 of 100 patients are cured and there are five deaths; however, the number of chronic cases remains the same. One sanatorium's records revealed that the number of patients with chronic disease (45 per cent of 300) was the same in both 1944 and 1954. Perhaps this figure remained the same because of frequent errors in therapy: The treatment was too brief or the rest periods were insufficient.

The rate of relapses, or new attacks of tuberculosis in a patient who apparently was cured, increased slightly prior to 1952. It reached 55 per cent in a survey of students and 25 per cent in a study of Parisian employees. In the past two years the rate of relapse has dropped to 20 per cent for those patients treated in a hospital; a relapse rate of 12 per cent was observed in sanatorium patients.

The number of primary infections has been declining. In young school children, the rate of reversal from negative to positive reactions to tuberculin skin tests dropped from 7.6 per cent in 1950 to 4.7 per cent in 1955. In Parisian dispensaries, pathologic primary infections decreased by one-third, although the number of consultations declined by only 12 per cent.

In spite of the progress already achieved, the mortality from tuberculosis still accounts for 12,000 deaths, which is four times higher than that in the Netherlands. Although this represents only 2.5 per cent of the over-all mortality, cases of tuberculosis constitute one-fourth of the long-lasting diseases and disabilities listed in the records of the French Social Insurance.

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SPAIN

Immunizing processes in cancer—In his initial lecture as a member of the Royal Medical Academy, Dr. Julián Sanz Ibáñez, Director of the Cancer Institute, stated that progress in immunizing technics and the development of other therapeutic procedures have opened broad new perspectives in the treatment of cancer.

One of the fundamental problems in treating tumors is to find substances which act selectively on tumor cells. Autoantibodies also must be considered. Pure and specific antigens must be obtained which provoke the formation of a great quantity of antibodies. These antigens must be as pure and specific as possible in order to avoid the introduction of substances which might cause antibodies to lodge in elements of the organism. If antibodies are obtained which act specifically to inhibit tumorous growth by integration in the tumor, it would be possible to associate these effects with those of their most persistent fixation in tumorous tissue to cause them to act therapeutically on the tumor alone or in combination with radioactive material. Beneficial results also could be attained by adding radioactive material to the protein component of the complement, which would serve as a carrier of radioactivity and would act at the point where the complement joins the antigen-antibody complex.

To further the study of immunizing processes in cancer, it is essential to develop the most favorable conditions for transplanting human tumors into animals. In concluding his lecture, Dr. Sanz Ibáñez referred to his experience with Estibil 430, with which he had produced sarcomas in mice and had maintained these malignant tumors for 12 years.

Psychologic Impotence

DONALD W. HASTINGS*

University of Minnesota Medical School, Minneapolis

Impotence usually is due to psychologic reasons, which range all the way from the fear of inexperience to profound disturbance such as homosexuality. The common psychologic background, however, relates to a basic difficulty in combining attitudes of love and affection with the physical aspects of the love relationship. Impotence will occur if the person loved is viewed as forbidden as a sexual object. Therapy for impotence of this type involves the attempt to change attitudes by means of psychotherapy; there is no known drug or surgical treatment.

IMPOTENCE is not a new problem or a symptom that has occurred because of the stresses of modern life. Myths and folklore relating to impotence go back to antiquity and make for a fascinating chapter in medical history. The many drugs and devices that have been used to treat this symptom are legion and range from oysters to powdered insects to yohimbine.

DONALD W. HASTINGS

Impotence is, by definition, the inability to obtain or maintain an erection satisfactory for sexual intercourse. The word "satisfactory" needs further definition in order to keep in mind the fact of individual difference. One might think that a man is partially impotent if his wife, having higher sexual drives than he does, desires relationships three times weekly but he is not interested this frequently (and is impotent on those occasions when he is not interested). However, he performs adequately at his own pace, perhaps once a week. This man is not impotent, but rather represents individual difference. The reverse situation, in which the husband has higher sexual drives than the wife but she performs adequately and with orgasm at her own pace, is also common; neither is this a frigid woman.

The process of erection is a complicated one and involves psychologic and physiologic interplay. It follows that trouble in either area

*Professor and Head of the Department of Psychiatry and Neurology, University of Minnesota Medical School, Minneapolis, Minnesota.

Presented before the forty-fourth annual Assembly of the Interstate Postgraduate Medical Association at Chicago.

(psychologic or physiologic) or in both could produce the symptom of impotence, and this is true. From a statistical standpoint, the great majority of impotence in the younger and middle-aged groups is due to psychologic causes. However, it is well to keep in mind that it may result from local and systemic disease. You are aware of the effects of certain neurologic lesions and debilitating systemic disease such as pernicious anemia. For reasons that are not clear, impotence may be an early symptom of diabetes. It is always well to keep chemical impotence in mind, and in this class the barbiturates are apt to be bad actors. The effect of the newer tranquilizing drugs on sexual potency is not yet known; it would be well to consider the possibility that they might affect potency, although I have not seen any reference in the literature to the occurrence of impotence with their use. Morphine addicts are usually impotent, as are chronic alcoholics, but the issue is not entirely clear here; emotional factors associated with morphinism and alcoholism may well be associated with impotence as well (for example, underlying homosexuality). I will talk more about drugs in a few minutes.

History

One point should be said at the outset about diagnosis, and it concerns history. An accurate sexual history is absolutely crucial to a correct diagnosis of impotence. This requires an unusually close and confidential relationship between patient and physician. Let me illustrate. One of the common forms of impotence, possibly the most common, is "selective" impotence. This term describes the man who is impotent at home but nowhere else, or who is potent at home but not outside the home—or whose impotence is some variant of these themes. Obviously, in either of these situations the man cannot have organic impotence and his trouble must have a psychologic basis. The physician will not learn of these diagnostic facts, as a rule, unless he has the absolute trust of the patient and a reputation for the strictest confidentiality. As another example, consider the man who marries in a sincere but misguided attempt to cure homosexuality. These are secrets that men are not likely to mention to a physician (or anyone else) unless they have complete trust and faith in the person to whom they are talking.

Let me say again, then, that an accurate sexual history is of critical importance to the diagnosis of the type of impotence, as will become clearer in the discussion of the various types. An accurate sexual history makes high demands on the physician for tact, confidentiality, and interview technic.

Classification of Impotence

There are a number of classifications of impotence. The one which follows is largely my own, and I make no particular claims for it except that of utility.

1. Impotence due primarily to organic causes
   a. Systemic disease
   b. Disease of nerve or blood supply
   c. Local disease of genitourinary tract
2. Impotence due primarily to psychologic causes
   a. Inhibition of normal potency
      (1) In the sexually immature
      (2) In the sexually mature
   b. Defects in psychologic development —"neurotic" impotence

Inhibition of Normal Potency

Inhibition of normal potency in the sexually immature male—By this is meant the common situation wherein a healthy young male at the outset of his sexual life finds that he is impotent on attempting his initial sexual experiences. This is the temporary impotence of inexperience, of guilt, of fear of discovery, of the inopportune situation. Ordinarily this type of impotence is overcome completely by accumulating experience, and only occasionally will this young man have sufficient anxiety to consult a physician. If he does, one can assume correctly that he has large increments of anxiety about his sexual failure, and the physician does well to keep this in mind.

Treatment for this young man will be that of listening seriously and attentively and of giving reassurance that the problem is a temporary one. A careful physical examination

which shows normal results is often the most powerful type of reassurance the physician can give. More often than not, this youngster is beset by old masturbation anxieties, and these tend to produce a large amount of open anxiety and fright. The youngster who has had a serious struggle with masturbation often fears he has damaged himself. An experience or two with impotence later on can easily revive these old fears, and he regards the impotence as proof of the damage he feared. In addition to a physical examination (which will in itself cause anxiety lest the physician discover the "damage"), there will be a good deal of reassurance for the patient if the physician discusses sexuality, spontaneously bringing up the topic of masturbation and stating that there is no known physical or organic damage that results from it.

If the patient has religious or ethical conflicts about masturbation (or any aspect of sexuality), the physician should advise him to discuss the matter with his clergyman. The physician, however, should feel perfectly free to tell his patient what is medically sound. He should not, in my opinion, inadvertently assume the role of minister or priest by implying that masturbation is perfectly all right, because such a statement may be directly opposed to the patient's religion. While on this topic, let me add that the physician also must tread carefully when a patient is reporting impotence at home but not elsewhere. Obviously this situation has important nonmedical components (ethical and legal). The physician does his best to avoid conveying the idea that extramarital affairs have either his approval or his disapproval. Making moral judgments about the patient is not, in my opinion, the doctor's job. The physician is an amateur in these matters; the clergyman is and should be the expert.

Inhibition of normal potency in the mature male—By implication, this is the impotent man who has been potent previously. This is too large a group to discuss adequately here, but let me make some brief remarks.

I have mentioned already the common problem of "selective" impotence. The man who has selective impotence is not impotent in the strict sense of the word, since he performs adequately under certain conditions. This situation reflects trouble at home, and the trouble almost always is a hostile relationship between husband and wife. If husband and wife carry chronic resentment and anger toward each other, it is understandable that they will have little if any sexual interest in each other. In this set of circumstances it is quite common for each to be carrying on a surreptitious affair with another sexual partner. Social circumstances being what they are, the woman is forced to do this more often in fantasy than is the man. Treatment of this condition obviously involves many factors. Once the diagnosis is determined accurately, the impotence (which may have been a sort of ticket to see the physician) fades into insignificance and usually is of no moment. Marital counseling, psychiatric outpatient therapy or both are indicated usually.

Bona fide fatigue is understandable as a cause of temporary impotence and may well occur in the executive who is overburdened by some set of business circumstances. If the patient ascribes chronic impotence to this cause, the physician does well to regard it as a rationalization. What the actual reasons may be becomes a problem in diagnosis.

Another subtype of this group is due to a depressive reaction. Impotence is often the first symptom to appear in a man who is becoming depressed, and it is often one of the last symptoms to leave after the depression has run its course. The impotence in depression probably is due to the overwhelming loss of interest that descends like a black cloud on every aspect of life. The patient has no more enthusiasm for sex than he does for golf, bridge, work, hunting or whatever his previous interests may have been. The point to remember here is that in a previously adequate man who is having a recently developed problem with impotence, depression should be included among the diagnostic possibilities. Treatment here is for the depression, not the impotence.

Chemical impotence—A few more words about drug or chemical impotence may be in order. Given a patient (for example, the busy

executive type) who is taking meprobamate during the day, liberal amounts of alcohol in the evening, and a greater or lesser amount of a barbiturate at bedtime, you have an excellent candidate for impotence. From a treatment standpoint, the physician has no alternative but to recommend abstinence from drugs and alcohol for a period, say a month, to find out if the impotence is chemical in nature. Such a period of abstinence will be difficult for the patient and may well be impossible. His ability to do it, or perhaps even to consider doing it, will depend on his motivation—on how big a problem the impotence is to him. It is one thing for the physician to recommend stopping drugs and alcohol, and quite another for the patient to be able to stop. The problem posed by telling a confirmed smoker to stop smoking or an overweight man to diet and lose 30 lb. is similar; you are all acquainted with the outcome of these medical suggestions. If motivation is low or absent (for example, in the case of "selective" impotence), the recommendation will fall flat.

As I mentioned before, this field is too large to cover here, but for those of you interested in reading about impotence and other sexual problems as well, let me mention the book "Sexual Hygiene and Pathology" by John F. Oliven, M.D. (Philadelphia, J. B. Lippincott Company, 1955). In my opinion this is the most mature book in its field.

Neurotic Impotence

The final category, "neurotic" impotence, describes the situation wherein psychologic potency never fully developed. The problem posed by homosexuality can be used to illustrate this group. If a man has little or no fundamental interest in the opposite sex, he is not apt to be potent. The mistake he sometimes makes is feeling that marriage may cure his homosexuality. It only increases the problem. Now married, he is locked in a sexual dilemma which only disturbs him more, and instead of finding marriage a treatment he finds it a serious problem. He may be able to have relations with his wife only by fantasying he is having relations with a man, and this is another disrupting factor.

Another type in this group presents an interesting problem. The symptoms are as follows. (1) The wish for sexual intercourse is present but the ability is not; (2) erections occur before or after but not during intercourse; (3) erections occur during heterosexual dreams and masturbation fantasy; (4) he cannot perform with a loved one but is potent with a downgraded woman, for example, a prostitute.

Here again one encounters a type of "selective" impotence, the difference being that this man has never been potent except with downgraded women. Freud considered this situation and expressed the opinion that the trouble lay in sexual psychologic development. Feelings of warmth and affection toward the mother are probably some of the earliest human emotions and are connected with acts such as feeding and cuddling. Direct sexual feelings develop much later and burst into full bloom during puberty and early adolescence. If one is going to be able to love his wife and also to be physically attracted to her, it follows that these two groups of feelings—the older ones of affection and the newer ones of physical sexuality—must be fused into a unit. If a complete lack of fusion exists, the man is condemned to a life of impotence with a loved one; she is too pure and untouchable to despoil sexually "as animals do" is often the train of feeling. However, physical sex is not barred with a woman he does not love and respect and hence it is permissible with a prostitute. The reason for this lack of fusion is thought to be psychologic in nature; an example is a mother who is frigid and paints sexuality as being morally wrong.

If the sexual history indicates that this is the type of impotence one is dealing with, I would recommend referring the patient to a psychiatrist. This is a character problem that will usually require prolonged and intensive psychotherapy.

This has been a brief description of the symptom of impotence. I hope I may have interested you to the point where you wish to read more about it, for the symptom of impotence can be a most distressing and devastating one.

The Red Eye

J. LEONARD SWIGERT* AND DUANE D. LAHEY†

University of Colorado Medical Center, Denver

Red eyes are caused by foreign bodies; acute congestive, chronic simple and chronic congestive glaucoma; acute iritis; and conjunctivitis, which may be bacterial, viral or allergic in origin.

Accurate diagnosis permits early and definitive treatment of numerous potentially serious threats to vision.

Signs and symptoms of the causative conditions are described, and preferred therapy is indicated.

THE general practitioner has the first opportunity to see and treat patients with a red eye. In this paper, we will briefly discuss the basic causes of this condition.

Foreign Body in the Eye

Perhaps the most common cause of inflammation of the eye is a foreign body embedded in the cornea, the palpebral surface of the upper lid, or the conjunctival cul-de-sac. The cure, of course, is first its recognition and then its removal.

The other principal causes of the red eye are glaucoma, acute iritis and conjunctivitis.

Glaucoma

Glaucoma in its various forms is the leading cause of blindness in the United States. Two per cent of all adults more than 40 years old have actual or incipient glaucoma. Acute congestive glaucoma has a sudden and dramatic onset, which is often precipitated by anger, emotional upset, or a prolonged period in darkness. The pain is intense along the distribution of the fifth nerve and is associated with marked prostration, nausea and vomiting. There is marked reduction in vision associated with the characteristic deep conjunctival, episcleral and ciliary congestion. The cornea is steamy, and it is often difficult to make out details of the iris and pupil. The pupil is usually dilated, and the intraocular pressure is markedly elevated. Treatment consists of immediate lowering of the intraocular pressure by vigorous use of miotics, DIAMOX®, sedation and, if necessary, surgery within eight hours. (Figure 1.)

Chronic simple glaucoma is insidious in onset with mild disturbances in vision as the only symptom. Routine use of the tonometer is the only way to detect this disease before

*Clinical Professor of Ophthalmology; †Chief Resident in Ophthalmology, University of Colorado Medical Center, Denver, Colorado.

J. LEONARD SWIGERT

DUANE D. LAHEY

irreparable damage is done. Many progressive general practitioners use a tonometer routinely and are highly gratified when they diagnose an early, previously undetected glaucoma. Some societies are conducting glaucoma-screening programs; this, together with education of patients, provides a productive field for preventing blindness.

Chronic congestive glaucoma produces mild symptoms including slight headaches, occasional halos, and transient blurring of vision. Provocative darkroom or mydriatic tests may be necessary to confirm the diagnosis.

The treatment of chronic simple and congestive glaucoma varies from lifelong use of miotic drugs to the use of various types of surgical procedures.

Acute Iritis

Acute iritis (iridocyclitis) usually has a gradual onset extending over a period of several days and associated with moderate reduction of vision, tearing and marked photophobia. There is usually severe pain in the eye with marked tenderness over the ciliary body.

TABLE 1

SIGNS AND SYMPTOMS OF PRINCIPAL CONDITIONS CAUSING RED EYE

	ACUTE CONJUNCTIVITIS	ACUTE IRITIS	ACUTE GLAUCOMA
Onset	Gradual	Gradual	Sudden
Local symptoms			
Pain	Burning, itching, foreign body sensation	Severe in eye and first branch of fifth nerve	Severe in eye and over entire fifth nerve
Discharge	Mucopurulent to purulent	Tearing	None
Tenderness	Slight	Present over ciliary body	Usually absent
Tension	Normal	Low or normal	Increased
Appearance of eye			
Conjunctiva	Superficial congestion, more marked toward fornix	Deep circumcorneal and ciliary congestion	Deep conjunctival, episcleral and ciliary congestion
Cornea	Clear; may have punctate staining filaments or erosions	Endothelial deposits	Steamy and insensitive
Iris	Unaffected	Markings are indistinct or muddy and vessels are visible; posterior synechiae	Congested, displaced forward
Pupil	Normal	Contracted or may be irregular	Dilated
Anterior chamber	Normal	Hazy from cells and exudate	Shallow
Constitutional signs	Absent	Slight	Prostration; nausea and vomiting may be present
Vision	Usually unaffected unless cornea is involved	Slightly reduced	Markedly reduced

(From Berens, C. and Zuckerman, J.: Diagnostic Examination of the Eye. Philadelphia, J. B. Lippincott Company, 1946, p. 132.)

Deep circumcorneal and ciliary congestion, indistinct markings of the iris, a contracted or irregular pupil, a hazy anterior chamber and, frequently, posterior synechia to the lens capsule are found. Systemic symptoms are mild, and the intraocular pressure is normal or lowered. Treatment consists of local and systemic administration of steroids and the use of mydriatics and sedation. The response is usually very satisfactory. (Figure 2.)

Conjunctivitis

Conjunctivitis has an onset of 24 to 48 hours, during which time there is burning, irritation, itching and the sensation of a foreign body, but no actual pain, as well as a mucopurulent to purulent discharge which causes the eyelids to stick together. The vision is not affected unless a secondary keratitis develops. The conjunctiva is inflamed, especially over the palpebral surfaces and in the fornices, with the congestion becoming less intense as the cornea is approached. The cornea is normally clear; however, in severe or long-standing cases there may be punctate staining of the cornea which is demonstrated with fluorescein. The iris and pupil appear normal, and the anterior chamber is clear and of normal depth. There is slight tenderness, and pressure on the eyeball usually does not elicit pain. (Figure 3.)

Numerous agents cause conjunctivitis. Bacteria are the most common causative agents, with *Staphylococcus* causing 85 to 90 per cent of cases. *Neisseria gonorrhoeae, Corynebacterium diphtheriae* (diphtheria), *Streptococcus Moraxella lacunata* (Morax-Axenfeld bacillus), *Pasteurella tularensis* (tularemia), and *Diplococcus pneumoniae* also produce the condition.

As better methods of isolating the agent are developed, viruses are becoming more widely recognized as causes of conjunctivitis. Trachoma, the leading infectious cause of blindness, is gradually being controlled in the United States. A few cases are found among the Navaho indians and among recent immigrants to this country. The disease is still rampant throughout Asia, the Middle East and North Africa.

FIGURE 1. Acute glaucoma, illustrating perilimbal injection, steamy cornea and dilated pupil.

FIGURE 2. Acute iritis, illustrating ciliary flush and miotic pupils.

FIGURE 3. Acute conjunctivitis, illustrating peripheral injection, clear cornea and normal pupil.

Adenovirus, of which 18 different types are known, causes:

1. Epidemic keratoconjunctivitis, a condition marked by an acute, often bilateral conjunctivitis which lasts about 13 days. In 80 per cent of cases, there is also corneal involvement consisting of central subepithelial infiltrates which clear in two to eight months.

2. Acute follicular conjunctivitis, an acute conjunctivitis with follicular hypertrophy which occurs five to seven days after contact and lasts four days to three weeks. In 50 per cent of cases staining corneal erosions with deep stromal edema are also present. All symptoms clear in 10 days to four weeks.

3. Pharyngoconjunctival fever, which has an onset nine days after contact which often is made at a swimming pool. The patient has a sore throat, fever and a conjunctivitis characterized by mononuclear cells in discharge. Preauricular lymphadenopathy and general malaise are common. The disease lasts from three days to three weeks, and the erosions of the cornea clear spontaneously.

Herpetic keratitis is the other severe viral disease which attacks the cornea especially. It produces a typical branching dendritic configuration which is brought out beautifully by a fluorescein stain. Serious visual sequelae may arise, and steroids should *not* be used.

Allergic conjunctivitis has a rapid onset and may produce itching and watering of the eyes, marked chemosis, follicular conjunctivitis, and a milky, sticky secretion loaded with eosinophils.

Inflammatory noninfectious disease is a hypersensitivity of tissues, which is probably due to tuberculosis.

The treatment of bacterial conjunctivitis consists of the administration of appropriate bactericidal drugs followed by local application of specific antibiotics. Systemic treatment with antibiotics also is in order. Boric acid or plain warm water should be used to cleanse the eye. Viral conjunctivitis should be treated by general supportive therapy, including mydriatics to reduce photophobia, the use of measures to prevent spread of the condition, and with broad-spectrum antibiotics to control secondary infection. Herpetic conjunctivitis is treated by cauterization and mydriatics; *no steroids* should be given.

The treatment of allergic conjunctivitis consists of avoidance of allergens, the systemic administration of antihistamines, local application of steroids, and, in mild cases, the administration of astringent drops.

Table 1 summarizes the signs and symptoms of the three principal conditions which cause the red eye. Accurate diagnosis and early and definitive treatment of these conditions will produce very gratifying results, including the removal of numerous potentially serious threats to patients' vision.

Diagnosis and Treatment of Allergic Angiitis (Anaphylactoid Purpura)

R. K. WINKELMANN*

Mayo Clinic and Mayo Foundation, Rochester, Minnesota

Diagnosis of allergic angiitis depends on clinical recognition of the entity and histopathologic examination of the skin. The cause is rarely identified.

Acute forms of allergic angiitis require vigorous treatment, including rest in bed; transfusions; removal of all questionable chemicals or drugs from the patient's environment and elimination of foods known to produce or aggravate the condition; antihistamine therapy, and usually steroid therapy.

In its chronic form, the disease may be managed conservatively.

A SPECIFIC type of inflammation localized principally to the small blood vessels of the skin has been described in recent years.[1-3] An intense, destructive vasculitis involves the subpapillary plexus of vessels and its extensions into capillary loops. The destruction of the vessel walls and the surrounding dermis, with resulting hemorrhage, produces clinical and histologic pictures that are both arresting and distinctive. The diagnosis depends on clinical recognition of the entity and histopathologic examination of the skin.

R. K. WINKELMANN

The cause of this vasculitis is rarely identified. Drugs account for most cases in which the condition is attributed to a specific agent. Sulfonamides and antibiotic, anticonvulsant and sedative medicaments are the principal offenders. A more recently recognized source of such a reaction is the group of environmental chemicals. I recently have seen cases in which this angiitis was secondary to exposure to chlordane and lindane, materials used extensively in insecticides, and to the widely used weed killer 2,4-D.

Farmers are using many chemicals to treat seeds, increase the growth of poultry, kill pests and control growth of weeds. Consequently, many of these environmental reactions will be found in the farm population. The relationship of such reactions to infectious processes has not been clearly established. Intradermal

*Section of Dermatology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

TABLE 1

SYNDROMES BASED ON NECROTIZING VASCULITIS

GENERAL SYNDROMES
Purpura rheumatica
Schönlein-Henoch syndrome
Allergic angiitis
Anaphylactoid purpura
Necrotizing vasculitis
Periarteritis nodosa of hypersensitivity
Wegener's granulomatosis
Lethal midline granuloma of the face
CUTANEOUS SYNDROMES
Acute parapsoriasis
Nodular allergid of Gougerot
Allergic granulomatosis
Allergic microbid
Erythema elevatum diutinum
Malignant atrophic papulosus (Degos)

TABLE 2

TYPES OF ALLERGIC ANGIITIS OF THE SKIN

ACUTE
Schönlein-Henoch syndrome
Acute parapsoriasis
CHRONIC
Papulopetechial type (trisymptom complex, or allergid of Gougerot)
Bullous, infarctive, purpuric type—allergic angiitis (tetra- or pentasymptom complex)
Persistent, symmetric, erythematous type (erythema elevatum diutinum)
Nodular, granulomatous type (may be acute but usually allergic granulomatosis)

reactions to bacterial allergens used for skin testing are increased in some patients who have this form of vasculitis. Streptococci have been related to some of the reactions by several authors.[4] It is well recognized that the Lucio phenomenon in leprosy is a form of vasculitis. I have seen one instance of such a cutaneous reaction secondary to the injection of bacterial desensitization products given for chronic sinusitis. Injections of protein may produce such a vasculitis. One such reaction following the injection of trypsin (PARENZYME®) has been observed. Foods, such as fish or lamb, apparently have a significant relationship to this process on occasions.

The onset of the clinical picture of cutaneous angiitis is abrupt. The episodes may be recurrent, and the lesions usually appear in crops. A remarkable characteristic of the cutaneous reaction is its symmetry. Whatever form the cutaneous picture presents, petechial or purpuric elements will appear. The petechial lesions are found in the more benign, chronic form. Purpuric and infarctive lesions occur in acute and more serious states of the eruption. On occasion, the lesions may be urticarial, vesicular, bullous or ulcerative.

The acute forms of the process may be characterized by a severe febrile response, migratory arthritis, headache, malaise and gastrointestinal discomfort. Hemorrhage may occur from the nasopharynx and from the respiratory, gastrointestinal and urogenital tracts. Occasionally, signs or symptoms of hemorrhage in the central nervous system are present.

The patient may give a history of allergic sensitivity to various medicaments, such as sulfonamides, antibiotics or barbiturates. A history of exposure to chemical agents may be obtained. At other times, a story of the injection of foreign proteins may be elicited. Laboratory findings of note are minimal. Normal platelet counts and blood-coagulation factors are important. The leukocyte count usually is normal or only slightly increased; there may be eosinophilia. The erythrocytic sedimentation rate may be increased. Evidence of visceral bleeding may occur, such as microhematuria or positive results of guaiac tests on stools.

A number of eponyms have been used to describe this clinical entity. In general, they have come into existence to describe different clinical forms of the same basic pathogenetic mechanism. A list of some of the terms that have been used in the past is included in table 1, which is a condensed list and is intended only as a guide. Summaries of this problem may be found in the work of Miescher,[5] Duperrat[6] and Zeek.[7]

The purpose of this presentation is to group the clinical cutaneous entities that may be classified as allergic angiitis and to illustrate the clinical and pathologic findings. Table 2

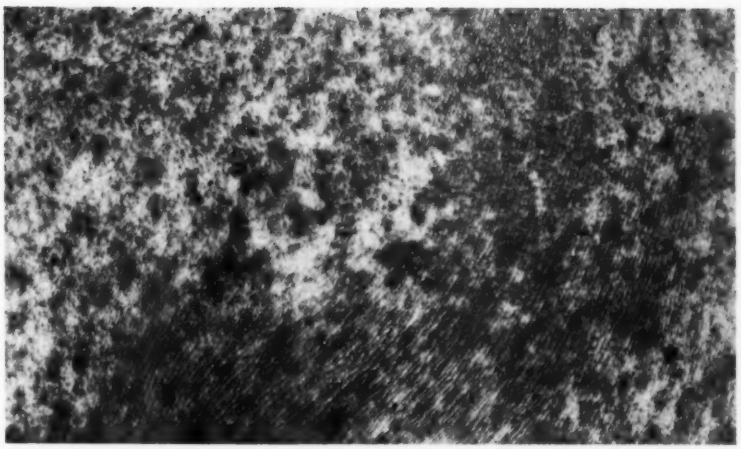

FIGURE 1. Macular, purpuric eruption of trunk that tends to become confluent, almost the same as does ecchymosis.

summarizes the acute and chronic reactions that may occur. The chronic reactions are important because of their benign prognosis. It is extremely difficult at times to make the diagnosis, and clinical recognition often is delayed in these cases.

Acute Angiitis

Two clinical forms of acute allergic angiitis exist. One is the classic Schönlein-Henoch syndrome, and the other is acute parapsoriasis and its variant, malignant papulosus.

The Schönlein-Henoch syndrome is a form of anaphylactoid (allergic) purpura that follows a fulminant course which may end in death. It is always accompanied by fever, arthralgia and malaise of various degrees. The bleeding associated with it is usually vigorous and often may lead to prostration and shock. Gastrointestinal bleeding has been considered as an important sign. The cutaneous lesions may be polymorphous, but a purpuric element always is associated with them. One may see a papulopurpuric eruption accompanying such a reaction (figure 1). However, erythema multiforme and urticarial reactions associated with purpura are more characteristic (figure 2). Large ecchymotic zones may develop in severe reactions. Signs of involvement of the central nervous system are not unusual, and cranial-nerve palsies often are associated. Massive bleeding from the respiratory tract is relative-

FIGURE 2. Urticarial and petechial lesions in acute generalized anaphylactoid hemorrhage.

FIGURE 3. Discrete, polymorphous eruption based on purpuric papules and eventuating in atrophic plaques.

FIGURE 4. Papulopetechial eruption. The recurrent crops of discrete lesions were notable.

ly frequent. Gross blood in the urine often is seen. This reaction is a widespread visceral and cutaneous vasculitis associated with massive hemorrhage.

Acute parapsoriasis, also known as pityriasis lichenoides et varioliformis acuta, or Mucha-Habermann disease, has been recognized only recently as a form of cutaneous vasculitis.[8] The clinical course is acute and benign, terminating in six to eight weeks. A papulopetechial, vesicular and necrotic polymorphous eruption occurs over the entire body. The eruption may be present in crops and at times is associated with mild constitutional symptoms and fever. Visceral bleeding has not been associated with it. A more recurrent and less acute form of this reaction has been recognized recently under the term "malignant papulosus (Degos)," [9] in which the vasculitis is associated with infarctive lesions of the intestine; in at least seven instances, this has led to death from intestinal obstruction. In the recurrent form, the cutaneous lesions proceed to atrophy and scar formation. The eruption may continue for a number of years

under these circumstances. Figure 3 depicts a clinical eruption associated with such a recurrent, acute, cutaneous vasculitis in which the lesions occurred over a period of three years.

Chronic Angiitis

Clinical forms of angiitis occur in which recurrent mild episodes are characteristic. Because it is accessible, the skin is the only organ in which such syndromes of chronic angiitis have been described. Four clinical types of chronic, cutaneous, allergic angiitis may be recognized. This differentiation is justified by the different prognosis of the several clinical varieties. However, any of these syndromes may show features of the others and may appear with features of acute angiitis. It should be re-emphasized that the many names used for this syndrome simply reflect the various groups of clinical characteristics that have been observed.

Papulopetechial type—This eruption is characterized by a symmetric, superficial, maculopapular and petechial eruption involving the lower part of the legs. It has been called the "nodular allergid of Gougerot" and the "trisymptom complex."[10] When viewed from a distance, it may resemble stasis dermatitis or senile purpura. The occurrence of petechiae within the papular lesions is a clinical indication of the true diagnosis (figure 4). This is a benign, episodic process. Patients who have this condition exhibit increased sedimentation rates, eosinophilia and microhematuria. It must be separated from purpura simplex caused by simple capillary fragility, which does not show vasculitis on cutaneous biopsy.

Bullous, infarctive, purpuric type—This is the type described in dermatologic literature as "allergic angiitis." European authors call it the "tetrasymptom complex" or "pentasymptom complex." Widespread, discrete, cutaneous lesions are found. Purpuric bullae are the essential lesions. Nodular lesions arise during healing. Infarction may occur because of the gross bleeding into the tissues (figure 5). While this eruption tends to be symmetrically disposed on the lower extremities, these lesions may occur anywhere on the body (figure 6). A high incidence of visceral bleeding is associated with this reaction, and thus the prognosis is more guarded than it is in other forms. Most of the patients have episodes over a period of several years, and the reaction eventually fades.

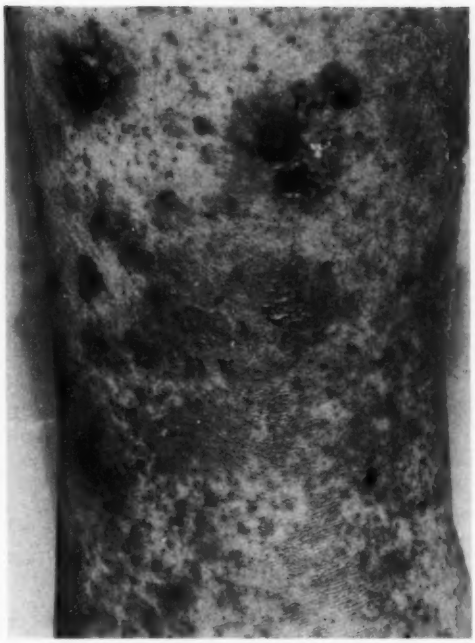

FIGURE 5. The bullous, purpuric form of angiitis on the leg. Note the central infarction produced by massive hemorrhage.

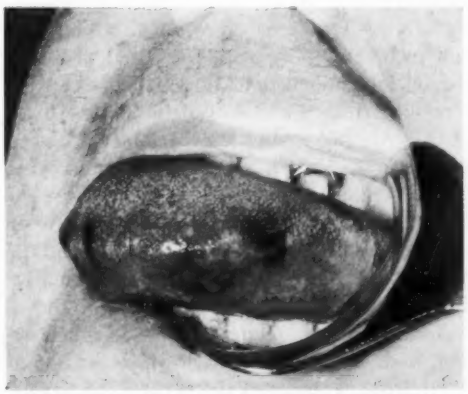

FIGURE 6. Hemorrhage in tongue in chronic angiitis.

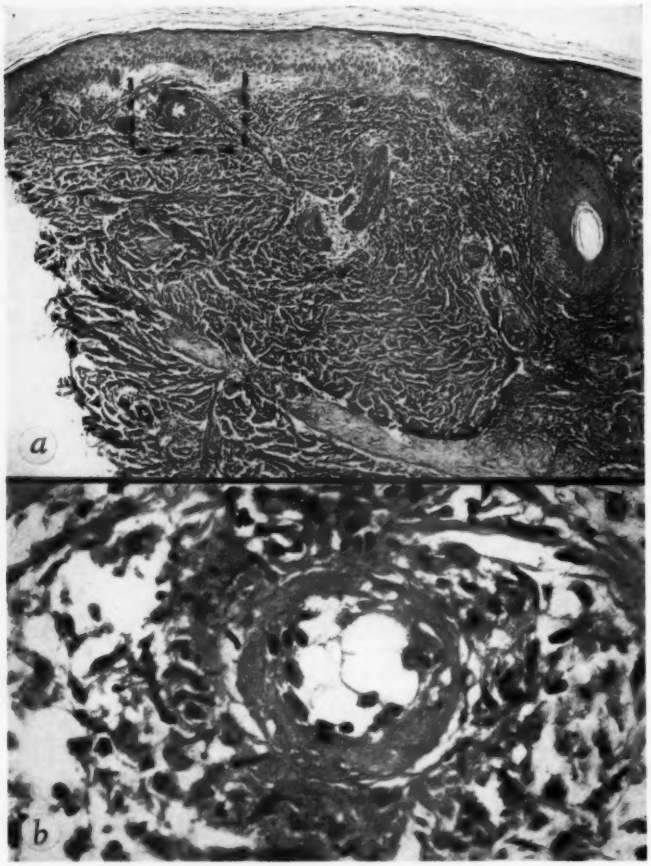

FIGURE 7a. Biopsy of skin, showing vasculitis of small vessels (hematoxylin and eosin; x 60). b. Thickened and hyalinized wall of the surface vessel marked in "a" (hematoxylin and eosin; x 500).

Persistent, symmetric, erythematous type—This form has been described in the older literature as "erythema elevatum diutinum." It is a recurrent form of angiitis that produces red to brown, macular to plaquelike lesions over the extensor surfaces of the body. In the more acute phase, the lesions may be associated with any of the findings accompanying the Schönlein-Henoch syndrome. After the acute episode passes, the patient is left with chronic dermatitis in the form of plaques. The histologic picture shows vasculitis, with hyalinization of the vessel walls.

Nodular, granulomatous type—In this eruption, nodular plaques, which may be annular or circinate, appear on the surfaces of the extremities. They usually occur later in the course of the eruption. The chronic, granulomatous, histopathologic reaction is described below. It has been stated that this reaction has a serious prognosis.[11] However, one patient I have seen was still well two years after his original episode.

Histologic Aspects

The vessels involved in allergic angiitis are uniformly small in diameter, with a minimal muscular wall. Only those vessels in the dermis of the skin regularly participate in the reaction; the large muscular vessels in the panniculus are not changed. Despite the fact that this reaction presents a common histologic picture, because most inflammatory diseases of the skin do produce a perivascular infiltrate,

the pathologic changes in vasculitis are immediately recognizable by the intense and severe nature of the reaction.

Acute angiitis may be accompanied by massive hemorrhage or dermal necrosis that obscures the underlying pathologic picture. In acute parapsoriasis, the epidermis and superficial dermis are the sites of acute inflammatory necrosis in which it is difficult to discern the individual elements.

The blood vessels show necrotic changes in their walls. The infiltrate in and about the vessel walls consists principally of polymorphonuclear leukocytes, with eosinophils being common. These leukocytes become fragmented and small amounts of nuclear debris accumulate (leukocytoclasis). Extravasation of erythrocytes is an important feature. Hyalinization takes place about and within the vessel walls (figure 7); this change is most apparent in patients receiving steroids, but it is not limited to this group. A wide band of homogenization of connective tissue may occur about the necrotic vessels. The epidermis may show necrosis and subepidermal bullae (figure 8). As the lesions continue, one may expect a histiocytic reaction to the amorphous necrotic material. The reaction may even form palisading granulomas, such as those observed in rheumatic nodules or granuloma annulare. It is this latter histologic picture that is seen in the dermis and about the vessels in the nodular, granulomatous type of chronic angiitis. It is reminiscent of the histologic changes in temporal arteritis.

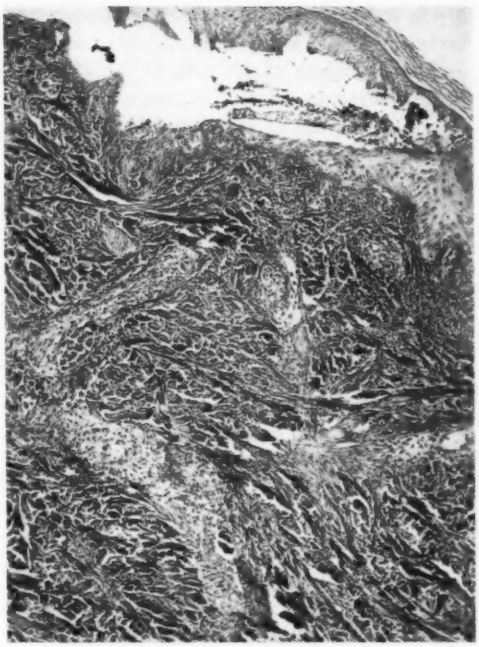

FIGURE 8. Necrosis of epidermis with bullous formation in dermal vasculitis (hematoxylin and eosin; x 65).

Diagnosis

The diagnosis is made by clinical recognition of a state of nonthrombocytopenic bleeding in which all the blood-coagulation factors are normal. While the cutaneous and visceral bleeding usually can be observed clinically, only microscopic examination of the urine or chemical examination of the stool will reveal it on occasions. Normal leukocyte counts may help in ruling out infections characterized by purpura, such as Rocky Mountain spotted fever. Eosinophilia and an increased sedimentation rate are useful findings. The simplest way to confirm the clinical impression is by cutaneous biopsy. The histologic changes can make the diagnosis.

Treatment

Acute forms of angiitis require vigorous treatment. All the indicated supportive measures must be given. The patient should be at rest in bed. Whole blood is often required when gross hemorrhage occurs. It is necessary to remove all questionable chemicals or drugs from the patient's environment. It is well to eliminate certain foods known to produce or aggravate such a state; these include cheese, fish, pork, chocolate, nuts, fresh fruit and tomatoes. Antihistaminic therapy appears to be reasonable, since these reactions are anaphylactoid in nature and since most cutaneous inflammation is accompanied by release of histamine. Long-acting antihistaminic agents can saturate the tissues effectively.

Steroid therapy usually is required. A simple way to use such measures without committing the patient to long-term hormonal ther-

apy is to administer adrenocorticotropic hormone (ACTH). Daily intramuscular or intravenous injections of 40 units of ACTH allow the physician to gauge the patient's response before a program of exogenous steroids is begun. In catastrophic situations, the daily intravenous administration of 250 or 500 mg. of hydrocortisone sodium succinate (SOLU-CORTEF®) or of 40 mg. of methylprednisolone sodium succinate (SOLU-MEDROL®) may be lifesaving. If large doses of oral preparations of steroids are needed, hydrocortisone is my choice. If moderate doses are used, methylprednisolone (MEDROL®) is satisfactory. Vascular reactions may occur with use of either triamcinolone or dexamethasone. Cutaneous purpura is frequent after the administration of prednisone. Once steroid therapy is started in the management of allergic cutaneous angiitis, it must be pursued as vigorously as it is in periarteritis nodosa. The program must be governed by the patient's response, as no more of the drug should be given than is required. In contrast to the situation in periarteritis nodosa, it is usually possible to decrease the amount of steroids given and finally discontinue their use within six months.

Chronic angiitis may be treated conservatively if the patients can be kept under careful scrutiny. A limited course of steroids or ACTH may be required to break the cycle of the reaction; however, antihistaminic therapy, rest and environmental control usually are all that is required to see the patient safely into remission. These patients should be observed at intervals, for they may experience recurrence. They are more susceptible than are average persons to the anaphylactoid type of reactions and should be warned about exposure to potentially harmful substances.

Summary

Acute and chronic forms of allergic angiitis (anaphylactoid purpura) have been described. The chronic forms involve the skin. The principal clinical sign is hemorrhage. Biopsy of the skin reveals characteristic necrotic vasculitis of the small blood vessels. Treatment may require use of steroids.

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Pregnancy Complicating Peptic Ulcer

WILLIAM E. CRISP*

The Lois Grunow Memorial Clinic, Phoenix

Recent reports suggest that there is no firm physiologic support for the clinical impression that pregnancy per se improves peptic ulcer. On the contrary, it can have a detrimental effect.

Four cases are presented to demonstrate that peptic ulcer can be aggravated during pregnancy and suddenly present its most severe complications of perforation and hemorrhage.

WILLIAM E. CRISP

THE physiologic gastrointestinal changes that occur secondary to pregnancy can exert a detrimental effect on a peptic ulcer. The clinical impression that pregnancy has a beneficial effect on peptic ulcer has led to a false sense of security concerning the dangers of peptic ulcer during pregnancy and a tendency to group all gastrointestinal complaints under the "dyspepsias of pregnancy." The case histories summarized herein demonstrate that during pregnancy a quiescent peptic ulcer can suddenly become active and present its most severe complications.

Case Reports

Case 1†—A 36 year old white multigravida was first seen in the third month of pregnancy. Her obstetric history was without incident except for a spontaneous abortion. Her medical history included an appendectomy and a duodenal ulcer of 10 years' duration which had responded well to medical therapy. The course of the present pregnancy was uneventful until the thirtieth week, when the patient complained of lumbar pain that radiated to the epigastric area. She had occasional nausea and vomiting during this time, but all symptoms responded to milk and a bland diet. During the thirty-ninth week she was awakened by severe mid-epigastric pain and vomited a large amount of coffee-ground material. This was followed by passage of a large tarry stool. The hematemesis and melena recurred several hours later, and the patient was admitted to the hospital in a state of shock. She responded well to blood replacement, but her condition was still consid-

*Section on Gynecology and Obstetrics, The Lois Grunow Memorial Clinic, Phoenix, Arizona.

†Presented through the courtesy of Anthony Ruppersberg, Jr., M.D.

ered critical when labor started. The medical and obstetric consultants felt that it would be safer to perform a cesarean section than to risk the hazard of transient hypertension which might occur during labor and reactivate the gastric hemorrhage. A meconium-stained, lethargic baby weighing 4,780 gm. was delivered. It did not respond well and died after 10 hours. The mother responded well to a strict medical regimen. The ulcer was demonstrated by x-ray.

Case 2—A 27 year old secundigravida had a four year history of periodic epigastric distress but an ulcer had not been demonstrated. During the last month of her first pregnancy the symptoms had been aggravated but had responded well to conservative medical therapy. The second pregnancy was uncomplicated until the thirty-sixth week, when epigastric distress recurred. This was relieved by antacids and small frequent feedings; despite this therapy the patient had a sudden episode of hematemesis and fainted. She responded well to blood replacement. The next day, spontaneous labor began and a normal baby weighing 1,910 gm. was delivered. The baby lived. The mother continued to respond well to medical therapy during the immediate puerperium.

Case 3—A 22 year old primigravida had an uneventful antenatal course except for attacks of nausea and epigastric pain during the last trimester. These complaints were ascribed to pregnancy. Delivery was normal. On the second day post partum she passed several large tarry stools and had subjective symptoms of acute loss of blood along with epigastric pain. Medical treatment for bleeding peptic ulcer was instituted, and there was no further evidence of bleeding or other symptoms. The ulcer was visualized by x-ray.

Case 4—A 28 year old primigravida, a nurse, was in good health until the twenty-sixth week of pregnancy, when nausea and nocturnal pain developed. Because of emotional and financial problems, these symptoms were treated with reassurance and AMPHOJEL®. They persisted intermittently until delivery, which was uncomplicated except for persistent epigastric pain radiating to the back. Two hours after delivery the mother suddenly felt faint, perspired profusely, and vomited a large amount of coffee-ground material. An active bleeding duodenal ulcer was diagnosed clinically and roentgenologically. The patient responded well to blood replacement and medical therapy.

Discussion

In the literature relating to the unusual problem of pregnancy and peptic ulcer the consensus is that the sum of the "anabolic processes" of pregnancy will improve peptic ulcers.[1-4] However, after a perusal of recent reports in the literature and based on a limited experience, this opinion is questioned. The incidence of peptic ulcer in women during the reproductive years is extremely low. There are no accurate statistics of the actual incidence of peptic ulcer in women of this age group which could confirm the clinical impression of improvement and therefore a decreased incidence during pregnancy.

Gryboski and Spiro,[5] reporting a study of blood pepsin levels during pregnancy as an indirect measure of gastric secretion, found no decrease in gastric secretion during the first two trimesters and a marked rise during the third trimester. Since peptic ulcer is directly related to the amount of hydrochloric acid and pepsin secreted, any rise in gastric secretion would tend to reactivate a peptic ulcer.

The origin of the rise in gastric secretion of both hydrochloric acid and pepsin during the last trimester of pregnancy is both humoral and neurohormonal. Dragstedt[6] demonstrated that if the emptying time of the stomach is delayed either by partial obstruction or by gastric atony, which occurs during the last half of pregnancy, there will be a prolonged or excessive secretion of gastric juice of humoral origin via the production of the hormone gastrin by the gastric antral mucosa. The neurohormonal phase of gastric secretion is mediated through the adrenal gland to the stomach by way of the hypothalamus and the pituitary gland.[7-9] Venning,[9] Gemzell,[10] Robinson and associates,[11] and Wallace and coauthors[12] have shown that there is a progressive rise in adrenal steroids during pregnancy, reaching a peak four times the normal level during the

third trimester and increasing to seven times the normal level in the immediate puerperium. Certainly this reflects the stress response of pregnancy.

Other studies of this adrenal-gastric relationship[13-15] have shown that a third phase of gastric secretion is under direct control of the adrenal gland. Numerous reports on the use of ACTH and the adrenal corticoids have confirmed the observation[16-18] that an increase in gastric secretion with resultant activation of an ulcer follows an increase in circulating adrenal corticoids.

Vasicka, Lin and Bright[19] reviewed these hormonal relationships and concluded that the adrenal-gastric relationship would cause a similar pattern of gastric secretion in a pregnancy associated with a peptic ulcer. They stated further that an individual variation of gastric secretion should be expected on the basis of the "permissive" and "conditioned" hypotheses of Selye[20] and Ingle.[21] Under normal conditions the stomach maintains a semi-autonomous role relative to the adrenal gland.

Conclusion

Recent reports in the literature suggest that there is no firm physiologic support for the clinical impression that pregnancy per se improves peptic ulcer. On the contrary, during the last trimester and the early puerperium a detrimental effect can be exerted on peptic ulcer because of an increase in the gastric secretion of pepsin and hydrochloric acid via humoral and neurohormonal mechanisms.

The subjective improvement of ulcer patients during pregnancy is probably a result of good antenatal care including instructions on the importance of frequent, regular feedings and a liberal intake of milk rather than of any direct anabolic effect of the pregnancy.

Persistent epigastric distress or heartburn should not be ascribed to pregnancy too readily. The possibility of an ulcer should be considered especially during the second half of pregnancy. In patients with a history of peptic ulcer, any digestive upset, especially in the third trimester of pregnancy or the immediate puerperium, should be considered of ominous portent and treated vigorously.

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Newer Antihypertensive Drugs

IRVINE H. PAGE*

The Cleveland Clinic Foundation, Cleveland

Even a little hypertension is a dangerous thing. The mortality and morbidity associated with this condition are now clearly apparent.

Specific treatment for hypertension has been developed within the last 30 years.

The first surgical procedures used were replaced by drug therapy; however, some agents employed produced iatrogenic diseases. Some of these drugs have now been discarded in favor of the ganglion-blocking agents and chlorothiazide. Two new drugs also appear to hold great promise.

When done with care in selected patients, vascular shunts and reparative vascular surgery have proved effective in lowering blood pressure.

The Early Days

IRVINE H. PAGE

THIRTY years ago when I started investigating hypertension, it was one of those diseases that had no repute; it was regarded as a sort of old-age phenomenon like arteriosclerosis. The infectious diseases were the important thing, and so the treatment of hypertension was "expectant" (whatever that meant), with "individualized nursing" (whatever that meant) and "study of the patient as a whole" (whatever that meant)!

Later, specific treatments were developed, such as anterior nerve-root section, which consisted of doing an unconscionably long laminectomy and then cutting the anterior nerve roots. However, such procedures were hard on the patient. I will never forget the first such operation I saw. Dr. E. V. Allen had told me about the original procedure, first done at the Mayo Clinic. I told Dr. George Heuer, at that time a new professor of surgery at Cornell

*Research Division, The Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute, Cleveland, Ohio.

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University Medical College, about this operation and he said, "I'll be glad to do one." I said, "Do you know how to do one?" He said, "No, but I'll do one anyway." So I said, "Well, wouldn't it be a good idea to go down and do one on a cadaver first?" He replied, "Oh, you don't have to do that sort of thing for surgery." So the next morning we did one, and I will never forget seeing that long laminectomy and thinking, "Where the devil are the anterior nerve roots?" Dr. Heuer looked at me and said, "Where are the anterior nerve roots?" I said, "Well, just turn the cord over and maybe we'll find them." He did and he found them.

The patient did beautifully. This was the first time I had ever seen the malignant syndrome reversed. The eyegrounds cleared within a matter of 10 days; renal function stopped falling and all was well. This was a great thrill to me. So far as I know it was the first patient in whom the malignant syndrome had been reversed.

Of course, as a therapeutic maneuver, this operation did not work out very well. There was a long period during which a variety of troubles occurred. There was also a great deal of discussion as to whether or not sympathectomy was any good. About 20 years later we decided we did not know how to select the patients who would benefit from the procedure. Had a real method been devised, I am sure the rightful place of sympathectomy would have been found.

Fifteen Years Later

Then began a period of drug therapy for hypertension. This era was quite fascinating, because each drug we used produced a new disease all its own. There was hexamethonium lung disease; the hydralazine or APRESOLINE® hydrochloride disease, which is like lupus erythematosus and rheumatic fever; the depression and parkinsonism resulting from reserpine, etc. While intriguing to us, this type of treatment was a little rough on the patients.

I found in Bennett Cerf's "Trade Winds" what I think is a perfect description of the way we used to treat hypertension. A bricklayer wrote this to the hospital authorities.

Respected Sir: When I got to the building I found that the hurricane had knocked some bricks off the top, so I rigged up a beam with a pulley at the top of the building and hoisted up a couple of barrels of bricks. When I fixed the building there was a lot of bricks left over. I hoisted the empty barrel back up again and secured the line at the bottom and then went up and filled the barrel with the extra bricks. Then I went to the bottom and cast off the line. Unfortunately, the barrel of bricks was heavier than I was, and before I knew what had happened the barrel started down and jerked me off the ground.

[This was the beginning of the treatment.] I decided to hang on, and halfway up I met the barrel coming down and received a severe blow on the shoulder. I then continued to the top, banging my head against the beam and getting my fingers jammed in the pulley. When the barrel hit the ground it burst its bottom, allowing the bricks to spill out. I was now heavier than the barrel so started down again at high speed. Halfway down I met the barrel coming up and received severe injuries to my shins. When I hit the ground I landed on the bricks, getting several painful cuts from the sharp edges. At this point I must have lost my presence of mind because I let go the line. The barrel then came down again, giving me another heavy blow on the head and putting me in the hospital. I respectfully request sick leave.

As you know, a wide variety of drugs became available during this period, and the problem of treatment assumed two different aspects. In the first place, for many years I have said that hypertension should not be treated until there is evidence of advancing vascular disease, because the drugs we had available were potentially dangerous, expensive and hard to handle. Therefore, I am not impressed with the idea that one should immediately start the treatment of hypertension on being notified of its presence.

I think many of you saw in the papers a report that verified something we have suspected for a long time; namely, that a little hypertension is a bad thing. I think it has now been incontrovertibly shown that even slight elevations in blood pressure do significantly increase human mortality. This is too bad, because it makes one wonder whether these little

"blips" in blood pressure which we used to ignore do not have some real significance.

On the other hand, it certainly does not suggest that with the drugs presently available we should start treating people with blood pressures of, e.g., 160/95. Such treatment very often only complicates a minor problem with iatrogenic disease. The sphygmomanometer has always made people fearful, but as someone said, "A person who is not neurotic these days probably is illiterate," so I suppose we are in for it, for better or for worse.

The substitution of pills for human philosophy during the treatment of chronic disease such as hypertension has never appealed to me. Hypertensive patients are frightened; they are fearful of their lives, and they have to live with the disease for most of their lives. Therefore, I think early in their management it is important to establish a relationship with them in which you will act as a support to them.

Let us not overlook the fact, however, that not all malignant hypertensions are due to some esoteric cause. Some cases of hypertension result from infections of the kidney, and penicillin is very useful in their treatment.

Ganglion-blocking agents can, if used persistently in large doses, reduce man's state to zero entropy. They can produce parasympathetic paralysis, a dry mouth, poor vision, achlorhydria, gastric distention, constipation, flatulence, urinary retention and impotence. On the whole, the patient may have a miserable life.

I think we can sum up the multiplicity of ganglion-blocking agents by saying that any one of the newer ones is about as good as another. This is an awful thing to say because, as you know, they have been promoted commercially so actively; however, ECOLID® chloride and INVERSINE® hydrochloride seem (temporarily, at least) to be about the end of the line, unless someone comes up with a really new idea in ganglion blockade.

Apresoline has been the bad actor, in a sense, because, as you know, it has produced the Apresoline or hydralazine syndrome. If too much of it is given, it causes a collagen disease similar to lupus erythematosus and to rheumatic fever. However, in many patients, Apresoline is extraordinarily effective without causing trouble, provided the dosage is not too high (figure 1).

Twenty-five Years Later

During the next decade, reserpine became available. Reserpine is like money: It does not make you happy but it certainly quiets the nerves. This drug has been tremendously abused, as you well know. On the other hand, it is a drug of great interest. For instance, it causes a great reduction of the serotonin content of the brain; it is a tranquilizer and it produces depressions, sometimes of very severe degree. It also causes parkinsonism in some people. It, therefore, is not the simple drug that we thought it was, and it is not the ideal agent for treating patients in whom hypertension has only recently developed.

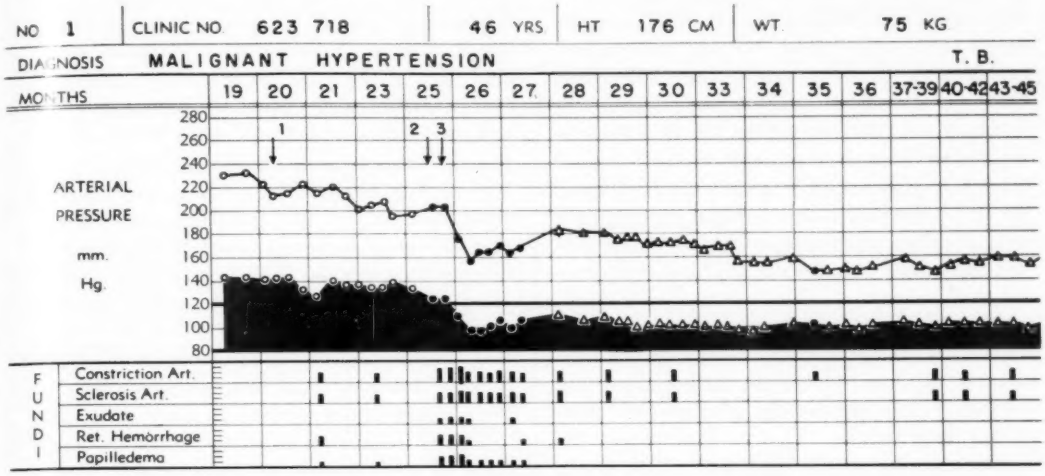
With all their disadvantages, these various drugs have nevertheless marked a significant advance in the treatment of hypertension. Before their introduction, we used low-salt diets. Some of the patients responded extremely well. When salt intake was reduced to 200 mg., blood pressure came down. When salt was readministered, the blood pressure went back up. People who responded that perfectly to the salt content of their diet were not usual.

We never could figure out who would respond to low-salt diets. There is salt in everything; thus, we were forced to conclude that these diets just were not very practical. There also was a period when the patient tried to take resins to avoid the low-salt diet, but the resins were worse than the diet.

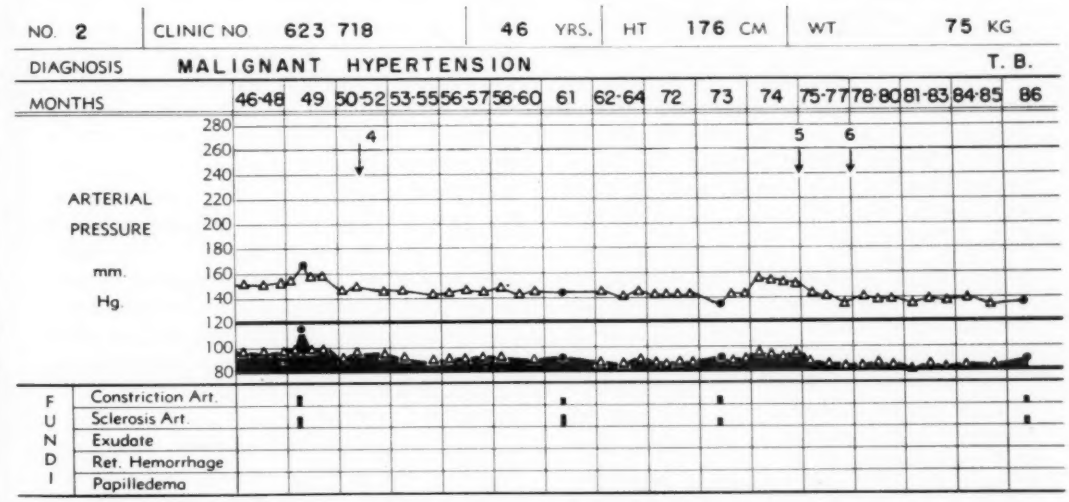
Thirty Years Later

When chlorothiazide (DIURIL®) was introduced, with almost one stroke the whole picture of treating hypertension changed. The amount of ganglion-blocking agent that was needed was drastically reduced when Diuril was given. One of the important effects of Diuril can be shown when the effect of hemorrhage or a ganglion blocker is studied.

Tetraethylammonium, a blocking agent, produces a sharp fall in pressure in normal patients. Following hemorrhage, such ganglion-blocking agents produce a much greater



1. DIBENZYLINE; 2. LONOLAC — LOW SODIUM DIET, DIBENZYLINE DISCONTINUED;
3. APRESOLINE



4. RAUDIXIN ADDED; 5. APRESOLINE DISCONTINUED;
6. APRESOLINE RESTARTED.

FIGURE 1. Chart showing results of long-term treatment of hypertension with hydralazine (Apresoline). At arrow No. 3, hydralazine was given and discontinued 50 months later. The blood pressure did not rise, and it may have remained normal without further treatment after so long a period of drug therapy. However, hydralazine was started again in a month.

The dots on the chart represent average blood pressures.

fall in blood pressure. In other words, when an individual's blood volume is reduced by a drug, ganglion-blocking agents or almost any other hypotensive agent, for that matter, lowers arterial pressure much more effectively than when such an agent is used alone. For instance, we knew during the war that the lowered blood volume of patients in shock caused the blood pressure to be extremely labile, and we had to be very cautious about moving such patients. This phenomenon is what we are taking advantage of in the use of Diuril or HYDRODIURIL®.

The basic actions of chlorothiazide are as follows. This agent first causes sodium loss, and sodium loss reduces the extracellular fluid volume, thus reducing the plasma and interstitial fluid volume. This in turn lowers the filling pressure on the right side of the heart, the cardiac output, and the arterial pressure. These results increase neurogenic constriction of the peripheral vessels, and since neurogenic tone is high, this increases the effectiveness of the ganglion-blocking agents. It is like cutting the switch when a lot of electricity is flowing, compared with the same procedure when little is passing. When the plasma volume and the interstitial cellular fluid are reduced, patients are very vulnerable to anything which depresses arterial pressure. By the device of lowering body sodium and blood volume, the iatrogenic diseases can be avoided because the dosage of the antihypertensive agents can be so drastically cut. It does not really make much difference whether one uses Hydrodiuril or Diuril. They are both effective; only the dosage is different.

I do not think the initial fears about chlorothiazide and hypokalemia have been justified. We were fearful that loss of potassium, along with the sodium, might cause very serious trouble. This is not to say that it cannot; it certainly can. However, after a couple of years of experience with this drug we do not see nearly as much hypokalemia as we thought we would. I think it is a fairly safe drug to use, recognizing that hypokalemia may result. A low-salt syndrome also occurs from time to time in patients treated with chlorothiazide.

I would like to tell you about two very new, promising drugs. The first is Guanethidine,* a drug which is not yet on the market. It is interesting because its action appears to be about halfway between that of hydralazine and that of the ganglion-blocking agents. It can produce severe postural hypotension.

Parenthetically, I should say I do not think postural hypotension should be included as one of the complications of a hypotensive drug. One of the best ways to reduce blood pressure is to stand up, particularly to stand up quickly. One can faint from sudden rising after lying in bed for a day or two without taking any hypotensive drug. It is little wonder that blockade of vasomotor compensatory reflexes withdraws the needed reaction when the force of gravity is exerted on the circulation.

One of the important things in the management of malignant hypertension is to get the blood pressure down and keep it down, because this will reverse the vascular lesions. Therefore, I feel very strongly that one should take advantage of the postural hypotension these drugs produce for the first few weeks until the vascular lesions begin to reverse. This is a critical period in the life of every patient with malignant hypertension, because renal efficiency can be lost in a matter of weeks. If that precious period when there is still reversibility is squandered by letting the patient get up and by not taking advantage of the postural hypotension, the patient's life may be lost. Do not be swayed by the youngsters on the ward who want to get these people out of bed; the patients are not going any place. They might just as well, in fact, they had better stay in bed; with the postural hypotension they get from these drugs, they won't be inclined to wander.

Guanethidine effectively lowers blood pressure in dogs with either neurogenic (figure 2) or experimental renal hypertension. It apparently does the same in patients, so far as we can tell, with about equal effectiveness.

Some people do not agree with me on this, but I feel that prolonged normal blood pressure is of vital importance to the malignant

*Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

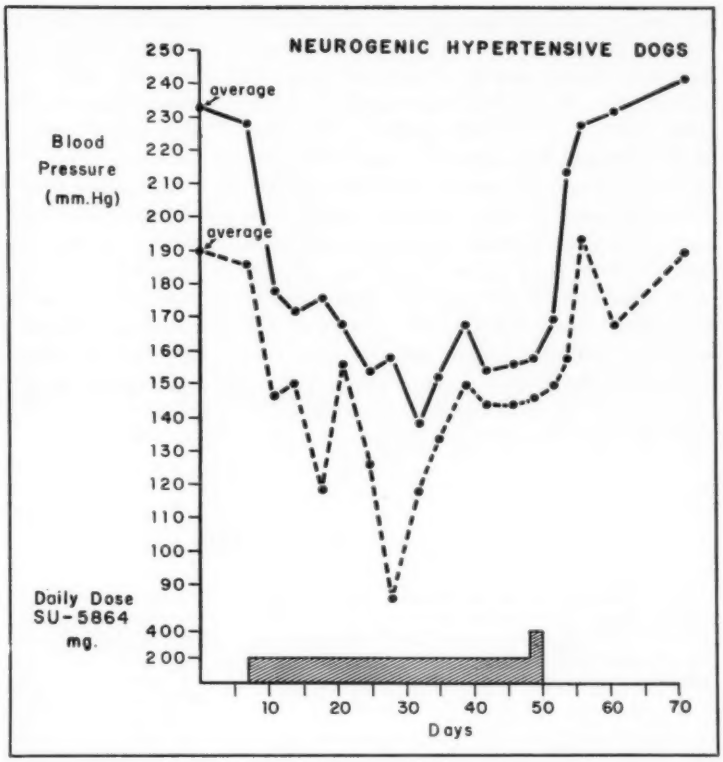


FIGURE 2. Graph showing the effect of daily doses of Guanethidine (19 to 63 mg. per kilogram of body weight) on a dog with neurogenic hypertension (buffer nerve section) and on another dog with renal hypertension (perinephritis elicited by cellophane).

hypertensive patient. As with the ganglion-blocking agents, this seems to be accomplished very well with Guanethidine in the relatively few patients in whom we have tried it. However, Guanethidine has the advantage in that it is much easier to handle and does not produce nearly as much dose sensitivity. Too much of a ganglion-blocking agent will really "clobber" the patient; with Guanethidine, there is much more leeway. On the other hand, it may be better to reduce the pressure initially with a ganglion-blocking agent.

We have not yet seen any toxic reactions to Guanethidine, although mild diarrhea is often encountered. In a few of the patients, there has been increased libido, which is a new turn in hypertensive therapy.

Another new drug, Daranthine,* has properties somewhat similar to Guanethidine, although chemically it is not too closely related. I do not believe it is on the market in this country, although it is in Canada. Daranthine is not too well absorbed; thus, large quantities must be given.

There now can be no doubt about the adequacy of the long-ignored, inexpensive chemical nitroprusside as an intravenous antihypertensive agent. It is too cheap to be a drug, but it works beautifully in the management of hypertensive encephalopathy. The pressures come down and stay down. As soon as the treatment is discontinued, blood pressure goes back up promptly. If this chemical is given for two or three days, hypertensive encephalopathy may be completely overcome.

Lastly, I think everyone is familiar with the fact that it is now possible by means of improved aortography to outline the renal vasculature with safety. For example, in our

*Burroughs Wellcome & Co. (U.S.A.), Inc., Tuckahoe, New York.

own experience, 27 per cent of our selected patients had renal arterial lesions. I am sure the figure among unselected patients would be much lower. With this large number of patients we are faced with quite a dilemma. Many surgeons feel that they must of necessity operate on such lesions. Not knowing the natural history of these vascular lesions, we have to be a bit careful in going ahead with some of these very major operations. On the other hand, the blood pressures have usually come down when the vascular shunts or the reparative vascular surgery suggested by surgeons has been done.

Now that we have much better drugs, we must ask ourselves what are the potential dangers of the operation itself and what may be achieved as a result of it and compare this with the effect achieved by the various new drugs. After studying the patient, we must decide which method of treatment is indicated for him.

There has been in the past 30 years a vast change in the management of hypertension. I think it is fair to say that we are probably at about the halfway mark in learning to manage hypertensive patients. This is becoming increasingly important, because we now recognize the mortality and the morbidity which are associated with hypertension. Therefore, I bring you a message which is in many ways of great cheer.

Books Received

Books received are acknowledged, and, as space permits, those of principal interest to our readers are reviewed more extensively. Reviews appear in this issue starting on page A-170; additional listings are on pages 479, 547 and A-182.

The Older Patient. Edited by Wingate M. Johnson, M.D., Professor Emeritus of Clinical Medicine, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina, with 21 contributors. 589 pages with 52 illustrations. 1960, Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. $14.50.

Essentials of Orthopaedics. By Philip Wiles, F.R.C.S., Lecturer in Orthopedic Surgery, University of London Faculty of Medicine, London, England. Ed. 3. 576 pages with 417 illustrations. 1959, Little, Brown & Company, Boston. $13.00.

Intussusception in Infants and Children. Pediatric Surgical Monograph Series. By Mark M. Ravitch, M.D., Associate Professor of Surgery, The Johns Hopkins University School of Medicine, Baltimore. No. 1. 121 pages, illustrated. 1960, Charles C Thomas, Springfield, Illinois. $9.00.

Psychiatry; Descriptive and Dynamic. By Jackson A. Smith, M.D., Clinical Director, Illinois State Psychiatric Institute, Chicago. 342 pages. 1960, The Williams & Wilkins Company, Baltimore. $7.00.

The Year Book of Pediatrics (1959-1960). Edited by Sydney S. Gellis, M.D., Professor and Chairman, Department of Pediatrics, Boston University School of Medicine, Boston. 493 pages with 119 illustrations. 1959, The Year Book Publishers, Inc., Chicago. $8.00.

Cancer and Allied Diseases of Infancy and Childhood. Edited by Irving M. Ariel, M.D., Associate Professor of Clinical Surgery, New York Medical College, and George T. Pack, M.D., Associate Professor of Clinical Surgery, Cornell University Medical College, New York, with 27 contributors. 605 pages, illustrated. 1960, Little, Brown & Company, Boston and Toronto. $22.50.

A Stereotaxic Atlas of the Dog's Brain. By Robert K. S. Lim, Ph.D. and Robert L. Moffitt, B. S., Medical Sciences Research Laboratory, Miles Laboratories, Inc., Elkhart, Indiana, and Chan-Nao Liu, Ph.D., Department of Anatomy, University of Pennsylvania School of Medicine, Philadelphia. 93 pages with 68 illustrations. 1960, Charles C Thomas, Springfield, Illinois. $9.25.

Textbook of Otolaryngology. By David D. DeWeese, M.D., Clinical Professor of Otolaryngology, University of Oregon Medical School, Portland, and William H. Saunders, M.D., Associate Professor of Otolaryngology, Ohio State University College of Medicine, Columbus. 464 pages with 354 illustrations. 1960, The C. V. Mosby Company, St. Louis. $8.75.

Basic Office Dermatology. By Stuart Maddin, M.D. and Julius L. Danto, M.D., Medical Staff, Vancouver General Hospital, and William D. Stewart, M.D., Clinical Instructor of Dermatology, University of British Columbia Faculty of Medicine, Vancouver. 308 pages, illustrated. 1960, Charles C Thomas, Springfield, Illinois. $11.75.

The Extremities. By Daniel P. Quiring, Ph.D., Late Head of the Anatomy Division, Cleveland Clinic Foundation, Cleveland. Edited by John H. Warfel, Ph.D., Assistant Professor of Anatomy, The University of Buffalo School of Medicine, Buffalo. Ed. 2. 120 pages with 106 illustrations. 1960, Lea & Febiger, Philadelphia. $3.25.

Diseases of Vasoconstriction

LEONARD D. ROSENMAN*

Mount Zion Hospital, San Francisco

Vasoconstriction of some degree is almost always present in the skin of the extremities; it is more active in peripheral sites. Vasoconstriction may be caused by stimuli of central origin or by reflexive responses to peripheral stimuli. Cold and posture are the most significant causes of reflexive stimuli. Abnormal vasoconstriction is seen in Raynaud's disease, post-traumatic dystrophy, certain occlusive diseases associated with inflammation, and Buerger's disease. Treatment consists of appropriate hygienic measures, drug therapy and sympathectomy, as indicated.

LEONARD D. ROSENMAN

BECAUSE of the historical confusion of etiologies, categories and treatment of disorders of vasoconstriction, it would seem logical in this discussion to establish a physiologic approach to these disorders and subsequently to define categories with overlapping boundaries into which to classify patients. The diseases that are described herein should be considered as such categories.

In diagnosing vasoconstrictive disorders, it is important to learn the clinical physiologic findings from the patient, as illustrated in the following cases.

Case Reports

Case 1—A woman of about 30 years of age had had troublesome bunions for many years. A year after surgery had been performed, examination revealed that the deformity of the great toes had been corrected. The patient stated that the wounds had healed promptly. However, from the time of surgery, her feet had been cool and moist. The skin of the feet and lower legs was mottled and generally bluish, and the toes, feet and ankles were almost always a little puffy. The patient also had poorly localized pain in the feet and ankles. This was an aching, sometimes throbbing, type of pain which was not relieved by mild analgesics. The pulses in all the arteries of the legs and feet were normal, and the patient had no

*Department of Surgery, Mount Zion Hospital, San Francisco, California.

evidence of other disease. She was an alert and intelligent woman who had become impatient with her discomfort.

Comment—The condition in this patient represented a mild continuous vasoconstrictive disorder. It is probable that she always had had a labile vasomotor apparatus. The system of sympathetic nerves which control the small arteries and veins in this patient was unusually sensitive to environmental stimuli. In an earlier generation, this was called a vasomotor neurosis. However, we must be careful not to imply that this or similar disorders are manifestations of emotional instability, anxiety or any other disorder which is currently considered of a neurotic nature.

The sensitive vasomotor apparatus in this patient was stimulated by one of several types of stimuli which ordinarily would not cause this response. The abnormal vasomotor activity may be explained as follows: The arterioles in the skin were constricted, slowing the flow of blood through the capillaries and venules of the subpapillary plexus; the tissues fed by the sluggish flow extracted more than the usual amount of oxygen from the blood. The venules as well as the arterioles, which are subject to vasoconstriction, were in spasm. The signs produced by these phenomena may be explained in this manner: The blue color of the skin was caused by the blue blood in the subpapillary plexus. The skin was cool because the radiator's inflow had been slowed. There was a little edema because the veins were narrowed and because there had been relatively more leakage than resorption from the capillaries. Because the same nerves which stimulated vasoconstriction also stimulated sweat glands, there was increased sweating.

There is no entirely adequate explanation for the pain with this type of vasoconstrictive disorder. The theory which I believe to be the most acceptable also explains why this disorder follows injuries. In the region of the trauma, small nerves are injured, but they are not divided. In the zone of the injury, the insulation that ordinarily keeps one nerve fiber from interfering with its neighbor is defective. Efferent impulses cross-stimulate afferent fibers, creating sensory disturbances and pain. It must be apparent at once that the autonomic fibers become offensive in the damaged nerve, because they have continuous, tonic efferent activity. Therefore, where there is increased vasomotor activity, there will be more cross-stimulation in the damaged nerves and thus more pain.

Had there been no history of trauma, this patient would have had a syndrome typical of acrocyanosis; however, because surgical trauma was a part of her illness, her condition may be classified as mild post-traumatic dystrophy.

The patient was treated with 25 mg. PRISCOLINE®, administered four times daily. Priscoline decreases activity in the autonomic ganglia. The patient noted improvement four hours after having taken the first tablet; by the second day, the coldness, clamminess and cyanosis had disappeared, and she had no more edema or pain or discomfort when walking. Treatment was discontinued after three weeks, and it will be resumed only if symptoms recur. A relapse is not likely to occur unless the patient has a new injury or becomes intolerant to the drug.

Case 2—A young woman, a physician in her mid 30s, complained of painful blanching of fingers. The first episode occurred while she was driving across the San Francisco Bay bridge one cool winter morning. The windows of her car were open; she was not wearing gloves, and the steering wheel was cold. Suddenly, the middle fingers of both hands blanched and became painfully numb. When she passed the toll plaza, the severe aching pain gave way to a sensation of burning, and her fingers turned a deep red. A little later, her fingers became blue and stiff, but they no longer were painful. A similar episode occurred a few days later, again while she was driving. This patient was in training psychoanalysis, a part of her preparation for a career in psychiatry. When she had difficult sessions, her fingers sometimes blanched. Between these episodes, her hands tended to be cool, but there were no other stigmata of vascular disease. When she immersed her hands in icy water, she also experienced blanching and aching pain, followed by reddening and burning pain, then by cyanosis and puffy stiffness.

Comment—The response to cold and sometimes to emotional upset caused the digital arteries of this patient's middle fingers to become so intensely constricted that all or nearly all the flow of blood to those fingers ceased. Ischemia of mixed peripheral nerves first caused loss of finer sensibility, then pain, and finally numbness. During the painful ischemia, enough products of local metabolism accumulated to overcome the constrictive stimuli. By the time the digital arteries opened, the vascular bed of the fingers was completely without tone, and the inrush of blood was in excess of ordinary vasodilation. With that reactive hyperemia, the skin was flooded with warm blood in sufficient amount to cause stimulation of the temperature receptors and sensations of burning. The atonic arterioles fed blood to leaky capillaries; a little puffiness resulted, and the fingers became stiff.

This patient had Raynaud's phenomenon, possibly caused by an unusual local sensitivity to cold or to circulating substances. Relief of symptoms followed the administration of 25 mg. Priscoline four times daily. The patient also was told to wear gloves, a hat and a scarf. Except for occasional episodes during skiing vacations, for which she resumes the medication, she has had no further recurrence of symptoms over a five year period.

Normal and Abnormal Vasoconstriction and Treatment

Where should the line be drawn between normal and abnormal vasoconstriction? Vasoconstriction of some degree almost always is present in the skin of the extremities; the more peripheral the location, the more active is the vasoconstriction. Only under conditions of high environmental temperatures, in high fevers, or during reactive hyperemia can we think of the absence of peripheral vasoconstriction. Therefore, with few exceptions, there always are stimuli for constriction of small arteries and arterioles and for the veins.

Some stimuli reach the vessels through the vasomotor nerves of the autonomic nervous system. The stimuli may be of central origin or they may come as reflexive responses to a peripheral stimulus. In emotional disturbances, there is a diffuse autonomic discharge, and peripheral vasomotor activity is seen. During yawning or sighing, transient vasoconstriction occurs. Certain lesions of the brain, particularly in the hypothalamus, cause vasomotor discharges. Other lesions in the gray matter of the spinal cord may do the same. A common example of the latter is the vasoconstriction often observed in extremities affected by poliomyelitis. It frequently is the only residuum detectable by ordinary methods of examination. This was illustrated in the case of a 29 year old matron with varicose veins who had a vein-stripping operation. During the immediate postoperative period, one foot became very dusky and cool, and the previously palpable pedal pulses were very weak. It was thought that the femoral or popliteal artery had been injured, until the patient awakened and reminded us that the leg had been afflicted with poliomyelitis during her childhood, and that whenever she became upset or chilled it would turn dark. Her recovery was uneventful.

Cold and posture are the most significant causes of reflexive stimuli. Whenever any part of the body is sufficiently cooled to permit return of cool blood to the vasomotor centers, peripheral vasoconstriction occurs. The tonic stimulus of cold continues until the blood is warmed. Posture as a stimulus to vasoconstriction occurs mostly in the legs. When one stands, the distention of the veins causes a reflexive vasoconstriction to lessen the puddling of blood in the dependent parts.

Local stimuli are agents which directly affect the smooth muscles of the smaller vessels, causing them to contract or relax. It has been noted that an accumulation of local metabolites causes relaxation of the restricted digital arteries. We also have observed the profound direct constrictive effect of cold on the same vessels. In emotional upsets, pressor hormones, particularly norepinephrine, cause vasoconstriction in addition to that caused by the sympathetic nerves. Other effects are recognized with a variety of drugs and hormones. In some persons, cooling activates certain globulins in the plasma which produce vasoconstriction.

It is apparent that one or several stimuli will predominate in some patients with abnormally intense vasoconstriction. However, we must remember that usually both central and local influences exist and that the effects are additive. In other words, we can seek to improve the disorders in several ways; for example, we may use a drug which acts in the autonomic ganglia to improve the symptoms of a vasoconstrictive disorder which seems primarily to be of local origin.

Raynaud's phenomenon—The most startling disorder of vasoconstriction is Raynaud's phenomenon, as seen in case 2, in which it possibly was caused by an unusual sensitivity to cold. In other cases, the defect seems to be one of vasomotor neural hyperactivity. When it occurs in rather severe and diffuse form—perhaps involving all extremities—in young women, Raynaud's phenomenon is called Raynaud's disease. Only when the digital arterial spasms are prolonged and frequent does ischemic damage to the tissues occur; this may be only atrophy, but occasionally it is local gangrene.

Treatment may be simple, as previously described, or the disorder may be so severe and diffuse that many forms of treatment will fail. What is said for treatment of one angiospastic disorder may be said for all, and the discussion of therapy in Raynaud's disease may be applied to other angiospastic diseases.

Obvious causes of the disease should be eliminated first. Tobacco in any form should not be used, as it is known that tobacco causes various amounts of vasoconstriction, probably in several ways. It may have a direct effect on the arteriole; it may stimulate the sympathetic ganglia, and it may act through the mechanism of deep sucking inspirations as does yawning. If the patient has a disease of "local fault" or a defect in the vasomotor neural apparatus, it matters little; he should avoid use of tobacco. The patient should attempt to lessen the effects of cold with "sensible" shoes, overshoes in the winter, hats, gloves, coats, and neck scarves. Occasionally, a move to a warmer climate is indicated. An effort to discover and to lessen emotional tensions is necessary in some cases, with treatment ranging from administration of phenobarbital to psychoanalysis. Vasomotor relaxants should be prescribed; many are available. If palpitations, dyspnea, giddiness or diplopia results from use of one drug, another should be tried. The dosages should be fairly large at first and then decreased if beneficial effects are achieved.

If the suggested measures fail or are intolerable, regional sympathectomy should be performed. There is no reason to accept sympathectomy as a measure of despair. In some patients it is curative, and in most it brings great improvement. Perhaps there is inadequate understanding of what to expect from sympathectomy. This procedure eliminates the vasomotor activity that has central or reflex nervous origin. Since there is some of that sort of activity in normal persons as well as in those with angiospastic diseases, eliminating the nerves will lessen the total of angiospastic influences. The same considerations apply to use of sympathectomy in treating arterial occlusive disease. In angiospastic diseases, the importance of sympathectomy is less disputable, even if the defect is not primarily neurogenic. However, if the disorder is reflexive or central in origin, sympathectomy may effect cure. The provisional word "may" is used because all the effects of sympathectomy may not be permanent.

In the lower extremities, a lumbar sympathectomy, which removes the second, third and preferably also the fourth paravertebral ganglia and their rami, nearly always is permanent. However, the denervated blood vessels regain some tone. After a few weeks, there is slight cooling below the levels of maximal vasodilation. The vessels retain their ability to contract in response to local stimuli and to drugs, but their sensitivity to cold does not equal the preoperative state, even after many years. With one exception, all these conditions are true of sympathectomy of the upper extremities. There is a greater problem of producing a lasting sympathectomy, of defeating the tendency for regeneration of fibers. Not one of the many technics which have been devised is entirely successful. In most cases, however, sympathectomy provides lasting

therapeutic success even though some regeneration occurs. I prefer ganglionectomy, unless the patient will be too disturbed by a Horner syndrome. In that event, an effort should be made to spare the ganglia, using a technic of ramisection.

Thus, in Raynaud's disease as in all cases of vasoconstrictive disorders, I recommend a program of appropriate hygienic measures, drug therapy and sympathectomy, using these measures in this order, as needed.

Post-traumatic dystrophy—The most common of all angiospastic conditions is post-traumatic dystrophy. Synonyms include reflex sympathetic dystrophy, Sudeck's atrophy and minor causalgia. In nearly all cases there is trauma (often a very trivial injury) and unusual pain, with vasoconstriction, sensitivity to cold, and mild edema. In many cases, the pain restricts activity of the affected extremity, leading to atrophy and stiffening of joints. Then, because of the weakness and stiffness, there is a cycle of secondary pain, disuse and further atrophy. Frequently, the patient seems unduly irritable and anxious. It is quite generally agreed that post-traumatic reflexive vasomotor defects are exhibited more frequently by persons who have a tendency toward emotional instability and neurosis. On the other hand, it is equally agreed that such neurosis does not underlie all cases and that in some instances the anxiety and disturbed emotions follow rather than precede the days or months of pain and disability.

Post-traumatic dystrophy usually can be diagnosed from the history and a simple examination. The role of reflexive vasomotor hyperactivity may be revealed by interrupting the sympathetic outflow. If the syndrome is discovered early, an injection of procaine into the regional sympathetic ganglia not only may provide a certain diagnosis, but also may cure the disorder. The use of vasomotor depressive drugs is rarely as successful as is the interruption of the sympathetics.

In addition to curing the initial injury, the goal of treatment is to interrupt the reflex sympathetic activity and to encourage active use of the parts to prevent or correct stiffness or atrophy. Occasionally, certain portions of the injured part in which pain is localized may be numbed by injections of local anesthetics. More often, it is necessary to block the sympathetics directly. If such a blockade with procaine has beneficial effects well beyond the expected duration of local anesthesia, the injection should be repeated. If the effects of the injections are brief, it is unwise to repeat them, and it is better to offer permanent sympathectomy by open operation. Of course, one must not forget the importance of persistent physiotherapy which emphasizes active motion rather than heat, massage, etc.

A patient whom I saw recently presented a good example of post-traumatic dystrophy. She was a 35 year old waitress who had twisted her ankle two and one-half years before. There was injury to the calcaneofibular and talofibular ligaments of a degree usually successfully treated by simple strapping. For two years after the first week following the injury, she had pain, stiffness of the ankle, and coldness of the foot. After seeking both medical and legal opinions without success, the patient finally saw an orthopedist who diagnosed the disorder. A lumbar paravertebral injection gave almost instantaneous relief of pain, and the patient walked without limp or stiffness during the following 20 minutes. When the effects of the procaine ended, the reflex sympathetic discharge was renewed, and symptoms returned. Therefore, a lumbar sympathectomy was done. The patient was reported symptom-free six months later.

It may be unwise to cite this case in relation to post-traumatic dystrophy, for after two years of disease, changes in joint capsules, tendon sheaths and subcutaneous tissues frequently are such that cure cannot be obtained simply by relieving vasomotor hyperactivity. It is better to treat the reflex disorder early, when perhaps an injection of trigger points or of sympathetic ganglia would suffice.

Post-traumatic dystrophy is observed after dog bites, sprains, fractures, infiltrated intravenous injections and other injuries. Mild symptoms go unnoticed. Some patients are labeled neurotic too early, and disputes over compensation lead to the perpetuation of the defect.

Occlusive arterial diseases associated with inflammation—In certain occlusive arterial diseases associated with inflammation, reflex or local vasomotor stimuli are prominent. Polyarteritis nodosa and Buerger's disease (thromboangiitis obliterans) may present acrocyanosis or even Raynaud's phenomenon. However, these diseases are not common in the ordinary practice. In any occlusive arterial disease, there may be significant vasoconstriction that adds to the ischemia. The collateral circulation and the vascular tree distal to an occlusion are small vessels subject to vasomotor activity. In many patients, release of the vasomotor activity is followed by improvement in the circulation beyond the occlusion.

Buerger's disease may occur in young white men of any racial origin. It is rare in women and even rarer in Negroes. It may affect the veins before it affects the arteries. The classic syndrome of occluded digital arteries, with extremely painful necrotic ulcers, occurring in young Jewish men is not the common form. It is true that when the smaller vessels are involved, there usually is pain in the nearby nerves; however, this picture often occurs after a series of other events.

Buerger's disease was diagnosed in a 39 year old man who had localized saphenous phlebitis in one calf in November 1957. In December another patch of phlebitis appeared in the right thigh, and later that month the femoral vein thrombosed, causing swelling of the entire leg. Then it was noted that in one leg the posterior tibial pulse was absent; in the other leg, there was no pulse of the dorsalis pedis. The left ulnar artery did not fill. It was notable that there were no symptoms of occlusive arterial disease, yet there were many symptoms of vasospasm. The patient's feet were clammy, cool and cyanotic, even in a warm room. On cool days, the coldness in his feet became uncomfortable.

The patient smoked 30 to 40 cigarettes a day; however, because he was convinced that tobacco in some way causes Buerger's disease, he was very willing to stop smoking. In the year after he stopped smoking, he had no lesions. However, the vasomotor hyperactivity continued, and it was not influenced by drugs. Therefore, to relieve the secondary angiospastic symptoms and to provide a more ample circulation beyond the levels of the occluded arteries, lumbar sympathectomy was done.

Briefly, the first step in the treatment of Buerger's disease consists of eliminating use of tobacco. Then treatment is the same as in all angiospastic or occlusive arterial diseases.

Postgraduate Clinical NOTES

133. ANTICOAGULANT DRUGS

The patient chosen for continuous anticoagulation therapy must be willing and able to follow instructions precisely, be conscientious in reporting any untoward incidents, and reliable in keeping all appointments.

He must be free of:

1. Disease compromising renal excretion.
2. Hepatic dysfunction.
3. Hemorrhagic diathesis.
4. History or demonstration of ulcerative disease of the gastroenteric tract.
5. Personality disorders (alcoholism, psychopathic personality, or suicidal depression).

Arthur J. Seaman, *Bulletin of the American Heart Association*, p. 555

The Diagnosis, Care and Prognosis of Atomic Injuries

SHIELDS WARREN*

Harvard Medical School, Boston

With the increasing use of atomic energy for industrial power, the likelihood of atomic accidents is becoming greater. The accidents which have occurred thus far in the atomic energy program have involved from one to eight men; in several, many more persons would have been involved if circumstances had been slightly different. Among the problems considered are external radioactive contamination, assessment of the degree of injury, and choice of therapy. With information now at hand, it would have been possible to save about half of the persons who died as a result of radiation at Hiroshima and Nagasaki.

SHIELDS WARREN

You probably wonder about the practical value of a discussion of atomic injuries. Dr. Rynearson† this morning stressed the importance of sometimes saying "I do not know," but one cannot say that too often; for if in your town or city you are unfortunate enough to have an atomic accident you ought to be able to do more than say "I do not know."

Just what is the likelihood of an atomic accident? Fortunately it is very slight, but it is increasing all the time. There are more than 60 operating reactors in this country now, and there will be many more in the foreseeable future. There are atomic submarines. There soon will be atomic merchant ships and naval ships. All these are sources of potential danger.

How does one recognize atomic injuries in the early stages? How does one determine how serious they are and what is going to happen? One of the first and most important things to

*Professor of Pathology, Harvard Medical School at the New England Deaconess Hospital, Boston, Massachusetts.

Presented before the forty-fourth annual Assembly of the Interstate Postgraduate Medical Association at Chicago.

†Rynearson, Edward H.: Practical aspects of the diseases of the pituitary body. To be published in POSTGRADUATE MEDICINE.

know is how much radiation the patient received. This can be determined partly by studying him, but practically every atomic plant has physicists and monitoring devices so that usually within two or three hours one can get an accurate estimate of the dose. As a rough rule of thumb from the prognostic standpoint, if the dose was more than 600 r you are not going to be able to do much for the patient. If the dose was less than that amount, you have probably better than a 50-50 chance of pulling him through, and if you pull him through he is going to do quite well.

One of the problems is to recognize by signs and symptoms whether or not the patient really is suffering from atomic injury—whether he has been truly irradiated by neutrons or gamma rays or merely "scared to death." At one accident there were several persons who received relatively minor doses of radiation, and none had serious, lasting effects, but the person who appeared the sickest, who vomited most, who started vomiting earliest (and these are regarded as significant symptoms) was the one who got the least radiation; he simply was more emotional than the others.

The questions to keep in mind, therefore, are (1) is this patient really irradiated, and (2) if so, how can I check from physical findings, from symptoms, the amount of radiation that the physicist tells me he received?

First, if the patient loses consciousness early, you can be sure he has received a supralethal dose of radiation and will be dead in a few hours. At Los Alamos about nine months ago, a man received approximately 10,000 r of radiation, became confused within a matter of a few minutes, lost consciousness, and then regained consciousness, only to die in a few hours. This is the overwhelming effect of radiation.

Second, the sooner nausea and vomiting appear and the more severe they are, the heavier was the dose the patient received. Unless the patient is fairly neurotic, he probably will not vomit unless he received a dose of more than 75 to 100 r.

Third, if diarrhea develops before 24 hours have elapsed, and if it is persistent and bloodstained, the prognosis is grave. The patient probably received a heavy dose.

Fourth, if the leukocyte count is seriously disturbed, the radiation dose was heavy. Initially (in the first four to six hours) there may or may not be a moderate leukocytosis. By six hours there will be a drop of the lymphocytes. By 18 to 24 hours the total leukocyte count will have dropped markedly, and if the radiation was severe the total count will be as low as 1000. If the leukocyte count does not decrease in subsequent days much below 1000, the patient probably will pull through. If the count goes to 500 or below, the prognosis is very serious.

Hemorrhagic manifestations do not appear early. They usually are delayed three, four or five days in the more heavily irradiated patients, and sometimes do not appear for 10 to 12 days. They will not appear if the platelet count stays above 20,000 or thereabouts. If the platelet count goes to 20,000 or below, platelet transfusions should be given promptly.

Anemia is late, not early. Not until the second or third week, or even later, do the erythrocyte count and hemoglobin level offer much help unless there has been such damage to the gastrointestinal tract that the patient is suffering from blood loss through ulceration or unless the fall in platelets is so severe that internal hemorrhage has produced anemia.

From the tenth to the twentieth day, something happens which scares the patient a great deal unless he is prepared for it, and that is epilation. The easiest test for epilation is to stroke the calves or the thighs. If the body hair comes away in your hand, there will be obvious shedding of this hair noticeable to the patient within, roughly, the next 24 hours. It is somewhat disconcerting for the patient to find much of his hair on the sheet or pillow in the morning. Fortunately, the hair usually regrows. Most of the patients that we found in Japan who had had epilation at the time of the bombings in 1945 had a good complement of hair once more by 1947.

In addition to direct atomic injury from the neutrons and gamma rays derived from the accident, there is also the possibility of some degree of radioactive fallout. This is not meant

in the sense of the stratospheric fallout that one hears so much about (and incidentally one need not be as afraid of it as some of the proponents of doom are inclined to say), but one must remember that there is a possibility that the patient's skin may be contaminated with radioactive material. This is particularly true if an atomic plant has been operated for some time prior to the accident. Fresh fuel elements, be they uranium or enriched uranium, are not as dangerous from the standpoint of radioactive isotopes as are those which have been operating a while, and spent fuel elements particularly are very rich in them and may be a potential source of danger. In addition to having one's physicist colleagues attempt to determine the acute dose received, it is best to have them check the patient with a radiation meter and determine whether or not there is contamination, which would result in skin or other damage.

Some of the natives of the Marshall Islands showed acute skin damage. Fallout from the atomic tests at Eniwetok came in contact with their skin and produced burns or ulceration. These fission products cause lesions much like second-degree burns, but if washed or rinsed off promptly do not cause difficulty. The Marshallese natives did not know what was happening, did not wash early, and consequently had these second-degree burns, which, however, were not too serious; somewhat later, only a few patches of loss of pigmentation were seen.

Let us say we have diagnosed a case of radiation injury and have estimated that the dose was 600 r. There is a chance to pull the patient through. What shall we try to do?

One of the very important things is that the patient needs rest. Many of the survivors of the bombings in Hiroshima and Nagasaki died later because they had to flee for their lives from the falling buildings, from the fires, and had to search the countryside to find food and shelter. Rest is of great importance and must be instituted relatively early.

If the patient is in shock, of course take care of the shock. Many of these persons may have secondary injuries of one type or another, either burns or traumatic injuries, and these should be cared for in the usual way with particular effort to guard against infection; with the loss of the white blood cells, infection will be very serious.

Give a bland diet. The entire mucosa of the gastrointestinal tract has been damaged. Among the most sensitive tissues in the body are those of the gastrointestinal tract, and these must be protected as much as possible. Consequently, give a bland diet, free of roughage. If the patient is seriously sick or is vomiting a great deal or has diarrhea, forget about the bland diet and depend on parenteral feeding. Later, as he improves, one can turn to utilization of the bland diet.

Since there are extensive ulcerations of the gastrointestinal tract with heavy radiation, and since the patient has impaired resistance to bacterial infection, the flora of the gastrointestinal tract is something to be concerned about. By and large it is better to have the carbohydrate-fermenting bacteria in the intestinal tract than others. Acidophilus milk, yogurt or something of that sort which will provide a carbohydrate-fermenting type of flora with relatively low pathogenicity is helpful.

If the platelet count gets close to 20,000 or drops below it, platelet transfusions are indicated. Whole blood transfusions are not quite as good, because the patients usually are not anemic early.

One must guard against infection and utilize antibiotics if there is any evidence of infection. It is preferable not to use the antibiotics prophylactically, because one may not be using the right one for the particular organism involved. By and large, penicillin is not too good to use because there may be problems of sensitivity. In the experimental animal, AUREOMYCIN® often is helpful.

If the hemoglobin level begins to drop seriously, it is time to think about whole blood transfusions. One does not need to bring the hemoglobin level completely back to normal. If one can keep it around 11 or 12 gm., this usually is adequate for the needs of the patient while at rest.

Bone marrow transfusion is the subject of a very appreciable degree of controversy at present. The survivors of the Yugoslav reactor ac-

cident who were cared for in Paris almost all received bone marrow transfusions. All but one are doing quite well. The survivors of the Oak Ridge accident, which was not quite as severe, received lighter doses of radiation and did not receive bone marrow transfusions; they all got well.

On the basis of what we know of transplantation immunology at the present time, we cannot expect bone marrow transfusions to be of lasting value unless truly matching bone marrow is used. There are approximately 32 serologic factors for which we can test at present on a practical basis. If as many as two of these 32 factors do not match, one will not get a satisfactory "take." Therefore, we have to say that the bulk of bone marrow transfusions will not "take" even from sibling to sibling or parent to child. Probably only in identical twins can one hope to make this technic work. If one were fortunate enough to have an identical twin available, then fresh bone marrow transplantation would be well worthwhile.

There probably is some transient value in the use of a single transfusion of bone marrow from a single donor if the patient is desperately ill. Multiple transfusions of bone marrow stir up what little immunologic response there may be, and then one has not only the problem of the patient's own antibodies getting in trouble with the transfused bone marrow cells, but also the different groups of transfused bone marrow cells.

There is some evidence that in animals, at least, transplantation of bone marrow has transient value by transferring some products of marrow cells, possibly of a hormonal or humoral nature (humoral probably rather than hormonal) that may have merit as a leukopoietic agent.

One could summarize the use of bone marrow transfusions by saying that if one had a desperately sick patient who had an identical twin, one could "shoot the works" as far as transplantation of bone marrow is concerned. If one had a seriously ill patient who did not have an identical twin, then a single transplant might be helpful. If the patient is not seriously ill, he probably will get along better without the bone marrow transplant.

Postgraduate Clinical NOTES

134. CARBON MONOXIDE POISONING

The severity of carbon monoxide intoxication depends on the degree of hypoxia and the duration of exposure. Patients with minimal degrees of exposure have severe headaches. Moderate to marked exposure may result in stupor or coma, complete recovery depending on the amount of cell damage. Patients recovering from coma have permanent neurologic changes. These range from blindness to Parkinsonism because of the presence of areas of cell destruction. If coma progresses to frank decerebrate rigidity, survival seems to be rare.

T. V. Craig et al., Hypothermia, its use in severe carbon monoxide poisoning, *New England Journal of Medicine*, October 22, 1959, pp. 854-856

Indications for Exploratory Surgery

WALTMAN WALTERS*

Mayo Clinic and Mayo Foundation, Rochester, Minnesota

Generally, the chief indication for exploratory abdominal surgery is an increasing amount of abdominal pain accompanied by loss of weight or changes in eating habits. Roentgenographic studies and clinical symptoms sometimes are misleading and result in erroneous diagnoses of abdominal conditions.

Surgical exploration frequently reveals unsuspected diverticula, benign lesions simulating malignant ones, scirrhous carcinoma, ulcers, or various biliary disorders.

Abdominal exploration is accompanied by minimal risk. In the author's experience, this procedure has revealed the presence of a lesion in 50 per cent of cases.

I SHOULD like to emphasize that an exploratory abdominal operation is indicated particularly when patients have an increasing amount of abdominal pain, the cause of which does not seem apparent. This is particularly true if patients also are losing weight or if they have changes in their eating habits, such as a sensation of fullness after eating, or loss of appetite. Obstinate constipation alternating with diarrhea and loss of weight with borborygmus also are suggestive of an intestinal lesion, especially if these symptoms are associated with anemia.

WALTMAN WALTERS

A particular type and location of pain are associated with cancer of the pancreas. This pain is epigastric, with extension through to the back. The patient feels better when he leans forward. More frequently, this type of pain afflicts men. It awakens the patient at night, and often it is difficult to control it by means other than morphine.

*Section of Surgery, Mayo Clinic and Professor of Surgery, Mayo Foundation, Rochester, Minnesota. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

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Abdominal pain which awakens the patient at night is almost always indicative of an intraabdominal lesion. Anemias of unknown origin, in the absence of blood dyscrasias, suggest a bleeding gastrointestinal lesion, as does, of course, vomiting of blood or the passage of tar-colored stools.

Now, that in essence is a synopsis of what I am going to say, but I have also chosen for mention a group of cases in some of which demonstration of the lesion was effected either by clinical signs or by the roentgenogram. However, I would point out that I have chosen lesions which are rather unusual and occur infrequently, and yet they often prove to be the ones which do not come to mind at the time one is trying to make a diagnosis before surgical exploration is considered.

We would all agree that it is not difficult, with the aid of the routine physical examination and history, our knowledge of disease, and the resources of the laboratory and roentgenography, to arrive at a correct diagnosis in most cases when the condition is clear-cut. Unfortunately, these are not the cases that are puzzling. The cases which baffle the diagnostician are the ones in which the signs and symptoms are those I have mentioned, and in which ordinary methods of examination or even very extensive detailed methods do not indicate the location of a lesion.

We shall proceed with this discussion and the particular points of importance from the standpoint of what abdominal surgical exploration might show, in addition to the indications for abdominal exploration.

Diverticula

The first patient in the group had a diverticulum of the stomach. Such a lesion always occurs on the posterior wall of the fundus adjacent to the cardiac orifice. This patient was 35 years of age. He had epigastric pain after eating. The roentgenogram disclosed the diverticulum only on a lateral exposure of the area. In the lateral view the lesion was seen near the esophageal gastric orifice.

I operated on this patient many years ago, but I was not able to find the diverticulum at the operation. The important consideration here was that the patient's pain continued. At a second operation I did find and remove the diverticulum and the pain was relieved. This is in the nature of a clinical experiment showing that these diverticula will produce epigastric pain, and if they are not seen roentgenographically—and often they are not because they are below or in back over the overlying stomach—they will be missed.

In another case, the diverticulum I removed demonstrated that such a lesion can be sizable. The patient's history gave a good idea of how these diverticula, when they become inflamed as a result of food retained in them, produce effects of gastrospasm. In addition, some diverticula bleed, and some patients thus afflicted have secondary anemia. This patient is a friend as well as a patient. I have been able to see her intermittently over the years. She has been perfectly well since the gastric diverticulum was removed.

You would think, from what you can see on a lateral roentgenogram, that it would be very easy to remove such diverticula through the gastrohepatic omentum on the lesser curvature of the stomach. This I have not found to be the case. They must be approached by dividing the lineal gastric ligament and by drawing the fundus and the greater curvature of the stomach toward the midline, so that the diverticulum is exposed. Moreover, the diverticulum, when not distended, does not project out from the stomach, because it is attached with the connective tissue to the posterior wall of the stomach.

Malignant and Benign Lesions

Let me speak for a few minutes of malignant lesions of the stomach which may have unusual manifestations. The only symptom may be a sensation of fullness after eating, with loss of weight. Frequently, the roentgenogram of the stomach may not be interpreted as showing a scirrhous gastric carcinoma. However, I think that if you will look at a roentgenogram of a stomach you will note that there is an absence of peristaltic waves and that the shadow of the stomach looks tubular. This is the characteristic roentgenographic picture of an extensive scirrhous carcinoma of

the stomach. In one patient such a roentgenogram previously had been misinterpreted as disclosing a normal gastric condition. This patient's history illustrated that in the presence of symptoms suggesting a sensation of fullness after eating or distress or loss of weight or anemia, even in the face of negative results of roentgenographic examination, one should carry out abdominal exploration.

Another patient had a benign gastric lesion simulating a malignant one. I shall not go into the details of this history because I want to bring out the important points related to the topic on which I am speaking. This patient had a loss of weight. There was little free hydrochloric acid in the gastric secretion after a routine test meal. The roentgenogram of the stomach seemed to show an ulcerating malignant lesion, and yet it was a benign lesion which simulated a malignant one.

Ulcers

In one man on whom I recently operated, the roentgenogram of the stomach seemed to indicate a scirrhous malignant lesion at the lower part of the stomach. The gastric deformity, however, was due to two penetrating benign gastric ulcers located in the pyloric area.

In this case, the roentgenogram appeared to show a duodenal deformity which was near the site of the sphincter of Oddi, suggesting a malignant process of this area which may develop without an obstruction of the biliary tract. However, malignant ampullary lesions may cause symptoms which suggest a benign duodenal ulcer, and that is just what this patient had—two benign ulcers. Yet, the deformity of the duodenum as shown in the roentgenogram would seem to suggest the presence of a malignant lesion situated around the ampulla of Vater.

In the next case, a penetrating duodenal ulcer produced signs and symptoms of cholecystitis. "Cholecystitis" in such a circumstance is a type of erroneous diagnosis that is made frequently. What actually happens is that penetration of the duodenal ulcer in the posterior wall into the head of the pancreas produces crisislike attacks of pain, and the edema around the area of ulceration in the head of the pancreas may sufficiently interfere with the passage of bile through the lower portion of the common duct for the patient to become jaundiced.

Consider the history of a patient who had an unsuspected gastrojejunal ulcer. What is the story and why is the error likely to arise in a case of unrecognized gastrojejunal ulcer? The confusion lies in the fact that an ulcer situated in the gastrojejunal stoma or in the stomach or jejunum adjacent to the stomach may bleed without causing pain, may perforate without previous evidence of a history of ulceration, or may obstruct. This set of circumstances may well give rise to error. Moreover, the roentgenologist, by virtue of the fact that the barium leaves the stomach so rapidly, is not able to identify a lesion in 50 per cent of such cases. What is to be done? The only course of action when this type of lesion is present is to rely on the clinical symptoms and your clinical diagnosis to indicate the need for surgical exploration.

Biliary Lesions

In our next case, pain in the upper right portion of the abdomen continued after cholecystectomy. If gallstones have not been present under such circumstances the inclination may be to call the condition biliary dyskinesia, spasm of the common bile duct, in a nervous woman; however, the fact may be that only partial cholecystectomy was performed and that a stone is present in a remnant of the gallbladder or in the common duct. Each year we see approximately 20 patients who have a stone or stones of some size in the common bile duct but who do not have stones in the gallbladder at the time of operation and whose cholecystograms disclose nothing abnormal. Now, since one-third of all stones in the common bile duct do not produce jaundice and two-thirds do not produce chills and fever, it follows that a third of such patients with stones in the common bile duct do not have symptoms of obstruction of the common duct, either jaundice or intermittent chills and fever, but they do have pain!

I recall one patient who had a markedly inflamed remnant of gallbladder with a stone in

it. In such a case, I think it is always best for us, for obvious reasons, in speaking with the relatives of the patient, to characterize the condition as a "dilated cystic duct," with inflammation and stone, rather than to say that incomplete cholecystectomy had been done previously.

Next, I want to mention intrahepatic cholangiolitic jaundice, which before operation is sometimes mistaken for extrahepatic obstruction. I have operated on four or five patients who had this type of jaundice. All of them had intrahepatic cholangitis, with bowel-pigment debris in the intrahepatic biliary canaliculi as shown in the microscopic examination of sections of tissue from the liver. Two of the patients had received chlorpromazine hydrochloride (THORAZINE®). One patient had taken only two tablets. She had been jaundiced for a few weeks. In spite of the erroneous preoperative diagnosis, after exploration of the common and hepatic ducts, T tube drainage of the common bile duct was instituted and the jaundice disappeared rapidly. Others have described similar cases. Possibly it is related to inflammation or dysfunction of the sphincter of Oddi in these cases, as well as inflammation of radicles of the intrahepatic biliary ducts.

Unfortunately, strictures of the common bile duct continue to plague us. On other occasions I have talked to you about stricture of the common and hepatic bile ducts and the methods of repair which my colleagues and I prefer, chief of which is to approximate the ends of the common bile duct after the stricture is removed. If this is not possible we have preferred the biliary-duodenal anastomosis, rather than the Roux-Y operation, because the biliary-duodenal anastomosis is easier and safer and the results are equally as good. In many cases, especially when previous operations have been done for the same condition, it can be done almost as a localized procedure without opening the general peritoneal cavity. If the patient bleeds or if leakage of the anastomosis occurs, the fluid drains to the outside rather than remaining within the patient's abdomen, producing peritonitis.

But there is another reason why we prefer biliary-duodenal anastomosis to the Roux-Y procedure in the repair of these strictures. Varco and his associates at the University of Minnesota Medical School carried out a parallel series of operations in which biliary-duodenal anastomosis was compared with biliary-jejunal anastomosis. They reported that in the 13 cases in which the biliary-jejunal anastomosis of the Roux-Y type was used there were two instances of the development of duodenal ulcer. The reason probably lay in the diversion of biliary secretion away from the duodenum. Yet, I have observed one or two such ulcers develop after the performance of biliary-duodenal anastomosis, too, so that diversion of biliary secretion cannot be entirely the cause. The point to remember, however, is that a duodenal ulcer may develop in a patient who has undergone any type of operation for the repair of stricture of the common or hepatic bile duct.

In one case, a patient had a stone of the common duct which was causing painless jaundice. A few minutes ago you heard me say that a third of the patients from whom I have removed stones of the common duct never have been jaundiced and two-thirds never have had chills or fever. These patients do have pain. There is, however, a very definite percentage of patients with painless jaundice in whom the obstruction is caused by a stone in the common bile duct, and such was the condition in the case to which I referred. Moreover, microscopic examination of tissue obtained by needle biopsy of the liver in these cases may show a hepatic or a cholangitic inflammation when, in reality, extrahepatic obstruction also is present. Abdominal exploration in these cases reveals the cause of the obstruction and allows it to be removed, if obstruction is present. Moreover, when there is any degree of jaundice it must not be forgotten that performance of needle biopsy is associated with a risk sometimes greater than that of abdominal exploration. My colleagues on the gastroenterologic service and the surgeons working in this field and I believe that in these cases it is often better to make a small abdominal incision to permit adequate inspection and palpation with biopsy of the liver

under visual controls, thus avoiding the possible leakage of bile into the peritoneal cavity, an action which may follow percutaneous needle biopsy of the liver in a patient who is deeply jaundiced.

In a patient on whom I operated, I overlooked a stone in the biliary tract. Whether it was in the lower part of the common duct or in the upper hepatic duct I do not know, but the routine postoperative cholangiogram, which I have always had made since 1936, showed a negative shadow in the lower part of the duct. The stones I removed from the patient's liver were high in bilirubin concentration. They were of the type which respond to fragmentation and solution by irrigation of the common duct with the alcohol-ether or chloroform mixtures. I used this mixture successfully on this patient, injecting it at first through the T tube and then removing the latter and immediately inserting a catheter down into the common duct through the fistulous tract made by the T tube. In this case the catheter went down into the lower end of the common duct and extended through the ampulla into the duodenum, pushing any little fragments of stone which remained. Dilatation of the sphincter of Oddi was present. An intravenous cholangiogram, taken later, showed that the common duct, although dilated, was free of any shadows cast by stones.

Comment

I have tried to show you and to give you a few brief examples of the value of abdominal exploration. I have not considered the small and large intestines, but, of course, abdominal exploration of these structures is equally necessary in order to determine the presence of some lesions.

It has been mentioned previously that whenever there is a question of an intraabdominal lesion it should be remembered that abdominal exploration is accompanied by minimal risk. With this I am in complete agreement, for in my experience abdominal exploration in 50 per cent of cases has been productive in disclosing the presence of a lesion. In half the patients concerned, the lesion was amenable to surgical treatment, and in the others x-ray therapy sometimes was shown to be definitely indicated and proved valuable.

Postgraduate Clinical NOTES

135. GASTRIC CANCER

The over-all five-year cure rate for patients with gastric carcinoma is currently less than 10 per cent, according to most studies. The highest is probably 14 per cent, as reported by the Mayo Clinic. At the Massachusetts General Hospital, the over-all cure rate for patients admitted between 1937 and 1941 was 7 per cent, in contrast with that of 12.9 per cent for patients admitted between 1947 and 1953. The reasons for this improvement have been studied by Welch and Wilkins, who found earlier diagnosis, extended use of surgical therapy, and more radical resections to be determinant. In the later series, the average time between appearance of symptoms and institution of therapy was four months as compared with five months in the earlier series.

Prognosis in gastric cancer, *Cancer Bulletin*, September-October 1959, pp. 82-85

Intestinal Obstruction Due to Volvulus of the Colon

KENNETH C. SAWYER,* ROBERT B. SAWYER
AND ROBERT E. McCURDY

University of Colorado School of Medicine, Denver

A survey of 276 cases of acute intestinal obstruction showed that volvulus was responsible for 8.6 per cent. Forty-six cases of volvulus of the colon are reviewed.
The authors feel that right hemicolectomy with ileotransverse colostomy is the procedure of choice in volvulus of the right colon; anterior resection with end to end anastomosis, whenever possible, is preferred in lesions involving the sigmoid colon.

KENNETH C. SAWYER

VOLVULUS is a torsion of the bowel on its mesentery which produces symptoms due to narrowing, strangulation or both.[1] The torsion or twisting of a segment of bowel obstructs the lumen and disturbs circulation to the wall of the intestine.[2] Volvulus of nearly all portions of the gastrointestinal tract has been observed and reported.[3,4] In 276 cases of acute intestinal obstruction we found volvulus was responsible for 8.6 per cent.[5]

Forty-six cases of volvulus of the colon encountered at Presbyterian Hospital and Children's Hospital, Denver, during the past 10 years form the basis of this report.

Incidence

The literature on volvulus of the colon[6-10] indicates that it is a rare cause of acute intestinal obstruction. Gerwig[2] pointed out the remarkable contrast between the incidence of volvulus of the colon in the United States and its incidence in Europe, particularly in the eastern and Nordic areas. He found, on reviewing publications by American and European authors, that in Europe 40 per cent of all cases of intestinal obstruction were due to volvulus, compared with 7 per cent in the United States. In Europe, 25 per cent of cases involved the small intestine, and 75 per cent the colon. In this country, 57 per cent involved the small bowel, and 43 per cent the large bowel.

In Europe, 33.3 per cent of the cases of volvulus of the colon involved the right colon,

*Associate Clinical Professor of Surgery, University of Colorado School of Medicine, Denver, Colorado.

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and 66.6 per cent the sigmoid. The maximal incidence of cecal or right colonic volvulus as a cause of obstruction is 17 per cent in Europe[11] and 5 to 6 per cent in the United States.[12] Volvulus of the transverse colon is extremely rare. We observed only one case in our study. The high incidence of right-sided colonic obstruction in our series is attributable to the large number of children included in the study.

Embryology

Ladd and Gross[13] described the normal process of rotation of the intestine as follows. "The alimentary tube grows at a faster rate than the celomic cavity from the sixth to the tenth week of embryonic life, and because of this, a portion of the midgut protrudes out of the abdomen into the umbilical cord. At about the tenth week, the peritoneal cavity grows more rapidly and the midgut is withdrawn into it. When the intestine recedes into the abdomen, it rotates in a counterclockwise direction. It is, therefore, evident that the postarterial portion of the midgut, which includes the terminal ileum, cecum, ascending and transverse colon, lies wholly in the left side of the abdomen. The rotation continues until the cecum comes to lie in the superior part of the abdomen. By the eleventh week of fetal life, the cecum and first portion of the colon are in the epigastrium. The cecum passes into the right upper abdomen and then finally ends its migration in the right lower quadrant.

"After rotation is completed, the cecum and the ascending colon attain peritoneal reflections and attachments in the right side of the abdomen. The mesentery of the small bowel likewise becomes attached to the posterior abdominal wall from the duodenojejunal junction obliquely downward toward the cecum."

Any departure from this normal process of rotation or any arrest in development during fetal life may result in (1) a nonrotated cecum or sigmoid colon, (2) failure of the mesentery to attach along the posterior abdominal wall, (3) a completely rotated but mobile and unattached cecum, (4) an obstructing duodenal band, or (5) a combination of these pathologic entities.

A volvulus usually owes its origin to a poorly fixed mesentery. For volvulus to occur, there must be one or two fixed points around which the bowel rotates. These often are congenital or acquired anomalies, although if the bowel is sufficiently mobile it can rotate around one of the normal ligaments in the mesentery or around one of the great vessels of the gastrointestinal tract.[1]

Wolfer, Beaton and Anson,[8] in an accurate anatomic study of 125 adult cadavers, found that in 11.2 per cent the cecum was mobile enough for a volvulus to develop. Instances of volvulus of the cecum have occurred in pregnancy,[14-16] during labor,[6] and in the postpartum period.[17] One case in our series occurred during labor, and one on the fifth postpartum day. Megacolon may play a part, and did so in two of our cases (figure 1). Some observers[18] believe that a vicious cycle exists in that attacks of volvulus of the sigmoid may give rise to megacolon, which in turn tends to result in volvulus less likely to undergo spontaneous reduction.

Miller and Clagett[19] stated that other causes might be violent peristalsis following heavy purgation or overeating, abdominal tumors, mesenteric cysts, fecaliths, foreign bodies, direct violence, and habitual constipation. Volvulus of the colon may occur postoperatively.[20]

Pathologic Process

The pathologic entities we encountered were exomphalos with no fixation of any portion of the gastrointestinal tract with volvulus, duodenal band with midgut volvulus, midgut volvulus, and volvulus of the sigmoid. In all cases, rotation was more than 180 degrees.

The circulatory change in the wall of the intestine in a closed-loop obstruction associated with volvulus is early venous occlusion, resulting in damage to the bowel wall and marked losses in blood volume from bleeding into the lumen of the intestine.[21] Pressure on the arterial supply to the bowel wall results in an exudation of serum into the lumen. Reflex arterial spasm[22] may account for the vast difference in the prognosis of a strangulated bowel resulting from arterial occlusion as contrasted with that of strangulation of the in-

FIGURE 1. Roentgenogram demonstrating volvulus of the sigmoid colon secondary to megacolon.

FIGURE 2. Barium-enema study depicting volvulus of the sigmoid colon.

testine due to venous occlusion. The viability of the intestinal wall is jeopardized further by distention which increases as the contents of the colon undergo fermentive changes, and the stretched wall of the distended colon loses its ability to absorb these contents. The colon becomes further distended from diffusion of blood gases, especially nitrogen, into the lumen. When the intraluminal pressure is greater than the pressure in the capillaries in the wall of the intestine, they are occluded and there is a diapedesis of intestinal contents through the wall and later frank perforation occurs with generalized peritonitis.

Symptoms and Signs

The symptoms and signs in our series were essentially those of intestinal obstruction and followed a rather constant pattern. Abdominal pain, vomiting and distention were the predominant symptoms. When the patients were older children and adults, there usually was a history of recurring attacks of cramplike abdominal pain, vomiting and constipation which had been present in varying degrees of severity throughout the patient's lifetime. In reports of right-sided midgut volvulus, some patients described episodes of violent abdominal pain with shocklike symptoms which were suddenly and spontaneously relieved before any diagnosis could be made. One patient had marked secondary anemia and always had been underweight. Dehydration, elevation of temperature, leukocytosis, abdominal tenderness and rebound pain were all observed. These secondary manifestations usually were proportional to the length of time the volvulus had existed.

Diagnosis

The correct diagnosis was made preoperatively in most cases in which the patients were infants. The radiology department was extremely helpful in establishing a correct diagnosis, and roentgenographic studies of the abdomen were made in all but two cases. The extent of the examination varied from a simple scout film to thorough studies of the entire gastrointestinal tract. In cases of chronic recurrent volvulus the results of barium enemas were sometimes misleading because the heavy barium stream produced a reduction of the volvulus.

Three-way abdominal roentgenograms can

FIGURE 3. Plain film of abdomen showing dilated ectopic cecum, distended loops of small bowel, and the ileocecal valve lying to the right of the cecum.

FIGURE 4. Barium contrast study portraying spiral distortion of the mucous membrane as seen in volvulus of the right colon.

suggest the diagnosis of volvulus of the sigmoid; however, contrast-medium studies are necessary for confirmation (figure 2). More difficulty is encountered in diagnosing volvulus of the midgut or right side of the colon. McGraw and associates[23] pointed out that the following observations from a film of the abdomen are significant, and these have been helpful to us.

1. The cecum is dilated and appears to be in an ectopic position (figure 3).

2. Loops of small bowel, distended with gas, may often be seen lying to the right of the cecum (figure 3).

3. The ileocecal valve may be demonstrated lying to the right of the distended cecum.

4. The spiral distortion of the mucous membrane sometimes may be seen at the site of the twisting (figure 4).

Treatment

Treatment of volvulus of the colon depends on its location and on the patient's general condition and the condition of his intestine and its mesentery at the time of operation. Volvulus in the right side of the colon presents a different problem from torsion of the left side of the colon. We used many operations to correct volvulus in both positions. Right-sided volvulus was treated with detorsion, appendicostomy, cecostomy, fixation of the right side of the colon, and resection of the postarterial portion of the midgut with primary or secondary anastomosis. Left-sided lesions were treated with detorsion, fixation, exteriorization, or resection with either primary or secondary anastomosis. A complementary cecostomy was used in most cases.

In reviewing this series, it was obvious that individualization was expedient in most instances. Because of the difficulty in fixing the right side of the colon to the right peritoneal gutter properly and because there were three recurrences of volvulus, we feel that in every instance except in children a midgut volvulus is best treated by resection of the postarterial portion of the midgut with primary closed end to end ileotransverse colostomy. The operation is mechanically sound and, contrary to many reports, we have not observed any ill effects from removing the highly absorptive ileal and proximal colonic segments.

TABLE 1

SITE OF VOLVULUS OF COLON AND COMPARATIVE INCIDENCE IN ADULTS AND CHILDREN IN 46 CASES

SITE	ADULTS	CHILDREN	TOTAL
Right colon	17	14	31
Left colon	10	4	14
Transverse colon	1	0	1
	28	18	46

Regardless of the procedure one chooses and regardless of the patient's age, care should be used in making sure that the band over the duodenum, which is often veil-like, is freed or divided adequately.

Volvulus of the left side of the colon presents a different problem because the fecal stream is solid, the colon often is greatly thickened and edematous, and the mesentery is woody and difficult to work with. At times it is impossible to accomplish a closed, aseptic anastomosis. For these reasons, primary detorsion and decompression with a rectal tube from below are the safest method for acute cases. Secondary resection can be accomplished when the colon is cleaned and decompressed. Where the viability of the bowel is questionable or the intestine is frankly gangrenous, it is necessary to perform an exteriorization procedure. This can be either the Mikulicz type or a Rankin decompression procedure. Occasionally it is possible to accomplish a resection with primary anastomosis,

TABLE 2

AGE DISTRIBUTION OF 46 PATIENTS WITH VOLVULUS OF THE COLON

AGE (YEARS)	NUMBER OF PATIENTS
0-1	14
1-10	4
10-20	0
20-30	6
30-40	3
40-50	4
50-60	7
60-70	5
70-80	2
80-90	1

TABLE 3

COMPARATIVE MORTALITY RATE IN ADULTS AND CHILDREN WITH VOLVULUS OF THE COLON

	NUMBER OF PATIENTS	DEATHS	MORTALITY RATE
Children	18	8	44.4%
Adults	28	1	3.6%
	46	9	19.6%

but it should be accompanied always by a complementary cecostomy.

In any procedure contemplated, a 5 per cent solution of neomycin injected into the lumen of the intestine minimizes secondary infection.

Results

Our group consisted of 46 cases of volvulus of the colon encountered at Presbyterian Hospital and Children's Hospital during the past 10 years. Eighteen (39.1 per cent) of the patients were children, and 28 (60.9 per cent) were adults (table 1). Seventeen of the children were boys, while in the adult group only 21.4 per cent were men. Thirty-one cases involved the right colon, 14 the sigmoid, and one the transverse colon. The large number of right-sided lesions is probably due to the large proportion of children in the group; 77.8 per cent of the children had lesions of the right colon compared with 60.6 per cent of the adults. Most of the cases of volvulus of the right colon involved the postarterial portion of the midgut (19 cases). The large number of patients less than one year of age (table 2) indicates the importance of the developmental defect in right-sided volvulus of the colon.

The left colon was involved in 30.4 per cent of the cases. These were most prominent in the adult group and were all limited to the sigmoid. We had one case of volvulus of the transverse colon, giving a 3.6 per cent incidence, which is consistent with that found in the literature.

Ten of the 31 cases of volvulus of the right colon were treated with right hemicolectomy and ileotransverse colostomy as a primary procedure. We feel that this is the preferable

method of management. Three of the 21 patients treated with reduction or fixation or both had recurrences, one died, and one required a right hemicolectomy with ileotransverse colostomy. Of the 14 who had volvulus of the left colon, four were treated with anterior resection, one was treated by fixation, reduction occurred spontaneously in two, one was reduced by sigmoidoscopy, and the remaining six were treated by detorsion and lysis of bands or adhesions.

The mortality rate for the entire group was 19.6 per cent (table 3), with the largest proportion of deaths occurring among the children, of whom 44.4 per cent died. The low mortality of 3.6 per cent in the adult group may well be due to prompt recognition and treatment and also to the fairly young age of the patients; the average age of the adult patients was 48 years.

Summary

A group of 46 cases of volvulus of the colon is reported. There were 28 adults and 18 children. This fairly rare cause of intestinal obstruction was more devastating in the latter, accounting for a mortality rate of 44.4 per cent compared with 3.6 per cent in the adults.

We have reviewed the incidence of this lesion and have discussed the embryology, the pathologic process, and diagnosis and treatment. We feel that volvulus of the colon is an important cause of intestinal obstruction which should be treated promptly and vigorously. In cases of volvulus of the right colon, we feel that a right hemicolectomy with an ileotransverse colostomy is the procedure of choice, and that an anterior resection with end to end anastomosis whenever possible is the procedure of choice in lesions involving the sigmoid colon. If the disease is suspected and diagnosed early in its course, treatment is satisfactory and mortality low.

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Peripheral Nerve Injury Associated With Fractures

KEMP CLARK*

University of Texas Southwestern Medical School, Dallas

The problem of combined injuries of the peripheral nerves and fractures of the long bones is covered from etiologic and pathogenetic points of view.

Principles regarding rates and times of recovery and methods of following rate of recovery are outlined.

Correct diagnosis is important so that adequate treatment, employing the principles outlined, may follow.

KEMP CLARK

THE peripheral nervous system is closely related anatomically to the bones of the extremities. It is surprising that the two structures are not injured concomitantly more often than they are. When combined injury does occur, it may present a rather perplexing problem in management. Attention to the known physiology of repair of peripheral nerves will enhance the results obtained in such wounds.

Pathologically, injured nerves, regardless of the precise mechanism of injury, will undergo a wide variety of changes. The nerve may grossly and histologically be intact, or there may be a total disruption of the nerve. If the axon fiber is severed, the nerve fiber will then undergo wallerian degeneration. This is characterized by loss of the axon fiber back to the nearest proximal node of Ranvier and by breakdown of the myelin sheath about the axon fiber. The development of collateral sprouting from the axon and the attempt of the fibrils to find the Schwann cell tube in the distal nerve trunk are the most pertinent parts of regeneration. Should the axon be successful, the axonal sprout will grow down the Schwann cell tube to the distal terminal ending of the nerve. Myelinization will then occur. and conduction will finally be re-established.

Such a sequence of events takes place only when the axon is destroyed. Physiologically, nerves may have conduction blocks which exist for a short period of time, and no anatomic change in the nerve fiber may occur. This is spoken of as neurapraxia. Injury of a

*Division of Neurosurgery, Department of Surgery, University of Texas Southwestern Medical School, Dallas, Texas.

greater degree will result in disruption of the axon fiber, but the coverings of the nerve remain intact. Such a nerve would appear in anatomic continuity. However, wallerian degeneration occurs, and regeneration of the axon fiber must occur before conduction is reestablished. This injury is spoken of as axonotmesis. If the injury is more severe, both the axon and its supporting structures will be severed anatomically. This condition is spoken of as neurotmesis.

It is apparent that the treatment required for each of the lesions is somewhat different. Furthermore, the type of injury may produce various types of lesions within a given peripheral nerve. That is, neurapraxia, axonotmesis and neurotmesis may coexist in the same nerve. The understanding of these changes occurring in the nerve is important in the treatment of patients with peripheral nerve injury.

A simple clinical classification of peripheral nerve injury associated with fractures may be outlined as follows:

1. Compound wounds
   a. Injury from without inward
   b. Injury from within outward
2. Closed injuries
   a. Stretch injury of the peripheral nerve
   b. Laceration injury of the peripheral nerve
3. Delayed peripheral nerve injury associated with fracture
   a. Peripheral nerve injury due to scar formation about healing bone
   b. Peripheral nerve injury secondary to swelling about a fracture
   c. Laceration, contusion or stretch injury of the nerve secondary to manipulative repair of the fracture

The most frequent combined injury of bone and peripheral nerve occurs in cases in which a compound wound is due to a bullet or other penetrating fragment. This is a wound which occurs from without inward. In this circumstance, the peripheral nerve may be severed (state of neurotmesis) rather than contused or traumatized by the fractured bone. The management of such a wound is prompt debridement of the compound wound plus adequate exploration of the peripheral nerve. Adequate debridement of all muscle and skin and subcutaneous tissue must be carried out just as though no peripheral nerve injury coexisted. If the peripheral nerve is found in continuity, nothing further should be done to it. However, if the nerve is anatomically severed, the nerve may be repaired primarily by using meticulously placed fine silk sutures through the nerve sheath. Delayed suture after several days or weeks while other injuries are treated may be equally effective.

Compound wounds which occur from within, such as severe bending injuries of the extremity, in which the fractured ends of the bone pierce the skin, may also result in laceration of the peripheral nerve. Again, the treatment is prompt and adequate exploration plus debridement of the wound. If the peripheral nerve is found to be lacerated, it should be repaired, either as a primary procedure or after a few weeks have passed.

In closed injuries of an extremity, in which a fracture and peripheral nerve injury occur concomitantly, the problem is somewhat more complex. Ordinarily, if exploration is not undertaken, the presence of a peripheral nerve injury should not change the management. The peripheral nerve in this situation may be in a state of neurapraxia, in which case recovery will occur promptly. However, if the injury is a rather severe one, the fractured ends of the bone may actually have lacerated the peripheral nerve. This is a rare type of injury related to the compound wound in which the bone has pierced the skin.

In the second type of peripheral nerve injury occurring in closed wounds, the peripheral nerve is stretched by injuring force. This injury pathologically may be either axonotmesis or neurapraxia, but, because of the stretch mechanism, there is no isolated segment of injury. Rather, the nerve unravels like a rope, so that the fibers are interrupted at multiple levels over a considerable segment. Characteristically, patients who have this type of injury have an incomplete type of peripheral nerve lesion and characteristically show dissociated loss. There may be motor function loss and intact sensation, or a purely dissociated sensory loss may occur. That is, loss of

pain and temperature sensation with retained touch is present. The presence of dissociated loss in cases of peripheral nerve injury is evidence for the mechanism of injury. Recovery from this type of injury is usually good.

Difficulty lies in distinguishing peripheral nerve injuries which should be explored from those which can be safely observed. Certain facts are prerequisite to an understanding of the proper timing of exploration to this problem. First, a careful and thorough examination of motor and sensory loss must be made. This is to establish an adequate base line for future observations. If a state of neurapraxia exists, recovery will occur within a few days. The problem of distinguishing axonotmesis from neurotmesis depends on the rate and order of recovery of the peripheral nerve. It is of utmost importance that adequate examination indicate the level at which a peripheral nerve is injured. Knowing this, a time of predicted recovery of the proximal denervated muscle can be made. This proximal denervated muscle is the one just distal to the level of the severance of the nerve. Since the regenerating axon fibers grow approximately 1 in. per month, an estimate of the lapsed time before evidence of return of function in the proximal muscle is possible. After observation for this period of time, if there is no evidence of return of function in this proximal muscle, exploration of the nerve is strongly indicated.

The development of Tinel's sign is of little value as evidence of return of function of the peripheral nerve. This sign is the production of tingling paresthesias by tapping along the trunk of the peripheral nerve. This is indicative of regenerating axon fibers, but is not indicative of their number. Unless an adequate number of axons cross the area of damage in the peripheral nerve, functional recovery will not occur. Tinel's sign, when present, is indicative that the nerve is in continuity, but is not a reliable index of functional return. It is far better to follow the rate of recovery of the proximal muscle rather than to rely on Tinel's sign.

Delayed peripheral nerve injuries associated with fractures may develop because the nerve is incorporated in a scar or callus about the healing bone. This is a rather rare circumstance, but if it should develop the treatment is surgical transplantation of the nerve to a scar-free bed. This procedure should be done as soon as the diagnosis of peripheral nerve injury is apparent. Delay will only produce increasing constriction of the nerve and progressive loss of axon fibers. If delay is unduly long, there may actually be constriction of the nerve trunk of such a degree as to require resection and suture of the nerve. Simple neurolysis and transplantation of the nerve into a scar-free bed will avoid this complication. Furthermore, the recovery rate will be greatly enhanced if little axonotmesis has occurred.

Another cause of delayed peripheral nerve injury associated with fracture is ischemic change. This may be secondary to vascular compression in an extremity by hematoma and swelling. This usually occurs in a tight fascial compartment through which a peripheral nerve happens to run. It is of utmost importance that fractured extremities should be kept elevated above the level of the right side of the heart and that the distal portion of the extremity be checked repeatedly for the development of ischemic changes. If these should occur or if undue swelling of the distal portion of the extremity should occur, the circular bandages should be cut. If no relief follows, appropriate autonomic block with procaine hydrochloride should be done. If improvement does not occur promptly, incisions should be made and wide fasciotomies of the extremity should be used to prevent the occurrence of ischemic gangrene. This is a problem not of the peripheral nerve so much as of the vascular injury. Peripheral nerves withstand compression of a gradually developing type quite well. The development of paresthesias, tingling and weakness in the immediate postfracture period, which were not present before reduction or casting, is indicative of vascular changes. These changes require prompt and immediate attention.

Occasionally, the peripheral nerve will be injured in manipulative efforts to reduce or repair a fractured bone. This obviously ap-

lies more to open surgical procedures on the fracture than to closed ones. However, closed manipulation will occasionally produce laceration or stretch injury of a peripheral nerve. Care should be taken during reduction of a fracture not to overextend an extremity during reduction and thus produce a stretch injury of the peripheral nerve. Manipulation should be gentle to avoid laceration of the peripheral nerves. If open reduction becomes necessary, the major peripheral nerve trunks in the region of the operation should be identified and retracted visibly out of the operative field. It is easy to injure a peripheral nerve during operation if it is not identified and treated with the respect it deserves.

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BOOKS RECEIVED

Books received are acknowledged, and, as space permits, those of principal interest to our readers are reviewed more extensively. Reviews appear in this issue starting on page A-170; additional listings are on pages 454, 547 and A-182.

Encyclopedia of Medical Syndromes. By Robert H. Durham, M.D., Physician-in-Charge, Division of General Medicine, Henry Ford Hospital, Detroit. 628 pages. 1960, Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. $13.50.

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Roentgenologic Diagnosis of Congenital Heart Disease in Infants and Children

RICHARD G. LESTER,* LEO G. RIGLER† AND EUGENE GEDGAUDAS‡

University of Minnesota Medical School, Minneapolis

A radiologic classification is presented to aid in the preliminary separation of congenital cardiac anomalies into physiologic groups. Further analysis of findings in each group can be made to arrive at a specific diagnosis. In most cases a firm clinical diagnosis can be made from fluoroscopic and radiographic findings plus the other clinical data. In difficult or complicated cases or when surgical correction is contemplated, more specialized technics such as angiocardiography and retrograde aortography may be valuable. Some indications for the special technics are listed.

THE importance of early and accurate diagnosis of congenital heart lesions in children is now well recognized. The advent of modern cardiovascular surgery has changed the prognosis of such lesions from one of hopelessness to a point where it can be stated that the large majority of these patients are potential candidates for a curative procedure (table 1). That this area has changed so strikingly from the "hobby" of Maude Abbott to one evoking the intense interest being shown at present can be credited to those bold surgeons who showed the practical value of separating the multitude of lesions comprising "congenital heart disease."

RICHARD G. LESTER

*Associate Professor of Radiology, University of Minnesota Medical School, Minneapolis, Minnesota.

†Visiting Professor of Radiology, University of California, and Executive Director, Cedars of Lebanon Hospital, Los Angeles, California.

‡Formerly, Fellow in Radiology, University of Minnesota Hospitals, Minneapolis; now at St. Boniface Hospital, St. Boniface, Manitoba, Canada.

The radiologic examination in the diagnosis of suspected congenital heart lesions is of value in two areas. (1) In the initial work-up, conventional roentgenologic examination usually indicates whether or not an organic heart lesion is present and the physiologic variety of the lesion; it may provide, with the other basic clinical data, a working or even a firm clinical diagnosis. (2) In the study of the precise anatomy and physiology of the lesion, more detailed studies including retro-

LEO G. RIGLER

EUGENE GEDGAUDAS

grade aortography and forward and selective angiocardiography provide much additional information. In addition, information about the internal anatomy of the heart can at times be gleaned from fluoroscopic following of the catheter during cardiac catheterization.

The major purpose of this article is to indicate a method of evaluation of plain films and conventional fluoroscopic study of the heart and great vessels in children with congenital heart disease. The background of this method has been indicated in a previous publication.[1] Charts are presented which can act as a guide in evaluating the data presented on films and at fluoroscopy in order to arrive at a working diagnosis.

The radiologic data represent the most important information that can be obtained by the simple examinations available to the practicing physician before recourse to special procedures. However, these data can be interpreted adequately only when they are correlated with the other clinical data, including history, physical findings and electrocardiographic records.

Roentgenologic Classification of Congenital Heart Lesions

The most-used clinical classification of congenital heart lesions divides them into cyanotic and acyanotic types (table 2). The value of this method is that it divides the lesions into physiologic groups dependent on the presence of desaturated blood in the systemic circuit, namely, the existence of a right-to-left shunt. The disadvantages are threefold. (1) Since

TABLE 1

CLASSIFICATION OF CARDIAC LESIONS

A. *Cardiac lesions that can be corrected*
- Coarctation of the aorta
- Patent ductus arteriosus
- Interatrial septal defect
- Interventricular septal defect
- Atrioventricularis communis
- Pulmonic stenosis
- Total anomalous pulmonary venous return
- Tetralogy of Fallot (Lillehei procedure)
- Ruptured aneurysm of sinus of Valsalva
- Partial anomalous pulmonary venous return
- Aortic ring
- Cardiac tumors
- Aortic-pulmonic window
- Congenital ventricular aneurysm
- Mitral stenosis
- Aortic stenosis
- Trilogy of Fallot

B. *Cardiac lesions that can be ameliorated*
- Tricuspid atresia
- Tetralogy of Fallot (Blalock operation)

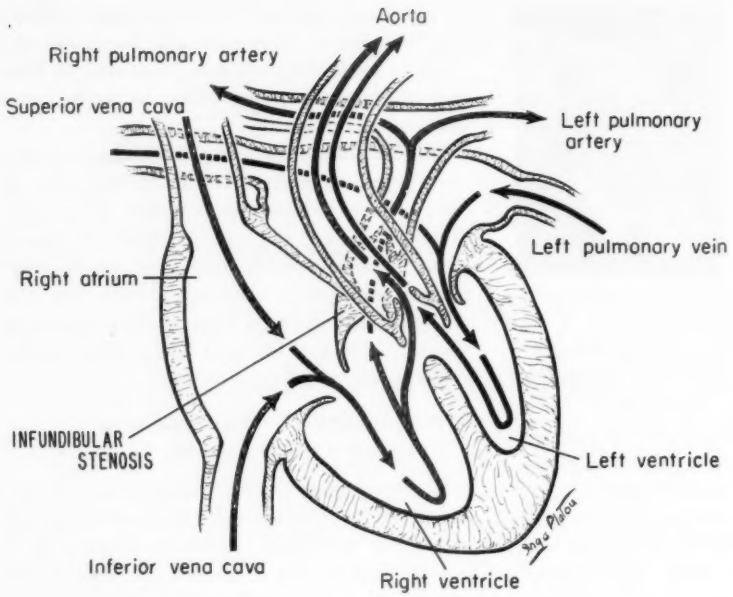
C. *Developmental*
- Transposition of the great vessels
- Single ventricle
- Mitral insufficiency
- Aortic insufficiency
- Ebstein's malformation

TABLE 2

CONGENITAL HEART DISEASE

A. *Clinical classification*
1. Acyanotic
   - a. Left-to-right shunts
   - b. Obstructive lesions
     - Left-sided
     - Right-sided
   - c. Myocardial lesions
2. Cyanotic
   - a. Right-to-left shunts
   - b. Admixture lesions
   - c. Bidirectional shunts with marked pulmonary hypertension

B. *Roentgenologic classification*
1. Increased pulmonary arterial vasculature
   - a. Left-to-right shunts
   - b. Admixture lesions
   - c. Bidirectional shunts with marked pulmonary hypertension
2. Normal pulmonary arterial vasculature
   - a. Obstructive lesions
     - Left-sided
     - Right-sided
   - b. Myocardial lesions
3. Decreased pulmonary arterial vasculature
   - a. Pulmonary obstruction with right-to-left shunt



TETRALOGY OF FALLOT

FIGURE 1.

approximately 5 gm. per cent of desaturated hemoglobin must be present in the circulating peripheral blood before cyanosis is evident, not all patients in the cyanotic group are blue. (2) Since other mechanisms for cyanosis exist in addition to the right-to-left shunt, some patients in the acyanotic group may be cyanotic. (3) Cyanosis is not a radiologic method of evaluation and may be difficult for the radiologist to appreciate, particularly when the patient is seen while the radiologist is wearing red glasses for fluoroscopic accommodation.

Consequently a roentgenologic classification (table 2) has been devised based on the pulmonary vasculature. This would include both the veins and the arteries of the lungs. Distention of the veins with or without accompanying edema must be sharply distinguished from dilatation of the arteries. The former is a sign of left heart failure commonly occurring in acquired heart disease. It may, however, be seen in certain congenital lesions, particularly subendocardial fibroelastosis as well as other myocardial lesions, and occasionally with coarctation of the aorta. We are concerned here essentially with changes in the arteries which are more characteristic of congenital heart disease. Thus, patients may be divided into those with arterial hypervascularity, normal vasculature, and decreased pulmonary arterial vasculature.

In cases with decreased pulmonary arterial vasculature there is a pulmonary obstruction combined with a right-to-left shunt (figure 1). All these patients are in the cyanotic clinical classification.

With normal vasculature there is no shunt (figure 2). These patients are in the acyanotic clinical group.

Increased pulmonary arterial vasculature may be based on one of three mechanisms. By far the largest group falls into the left-to-right shunt category (figure 3). These patients are acyanotic, as there is no desaturated blood in the major circulation. A second group comprises the admixture type, in which blood from both ventricles is mixed in a greater or lesser degree before entering the two circulations (figure 4). In a third variety, with a lesion that ordinarily would create a left-to-right

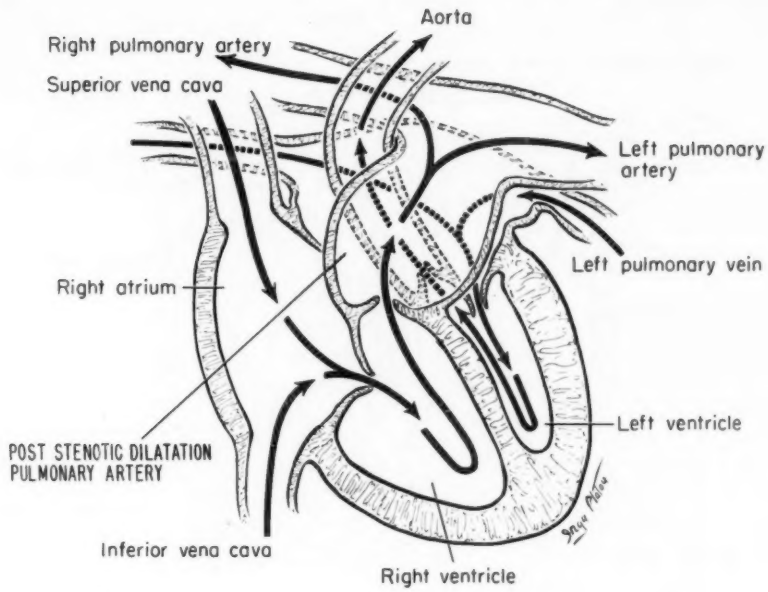


FIGURE 2.

ISOLATED VALVULAR PULMONARY STENOSIS

shunt, there is sufficient pulmonary hypertension so that a proportion of the blood reverses its flow to form a right-to-left shunt. Both these latter types are in the cyanotic group.

Table 3 shows the common lesions in each of the radiologic groups. Note that the four common left-to-right shunts make up about 50 per cent of all cases of congenital heart disease in children. Tetralogy of Fallot is the most common cyanotic heart lesion, and transposition of the great vessels is next in order of incidence.

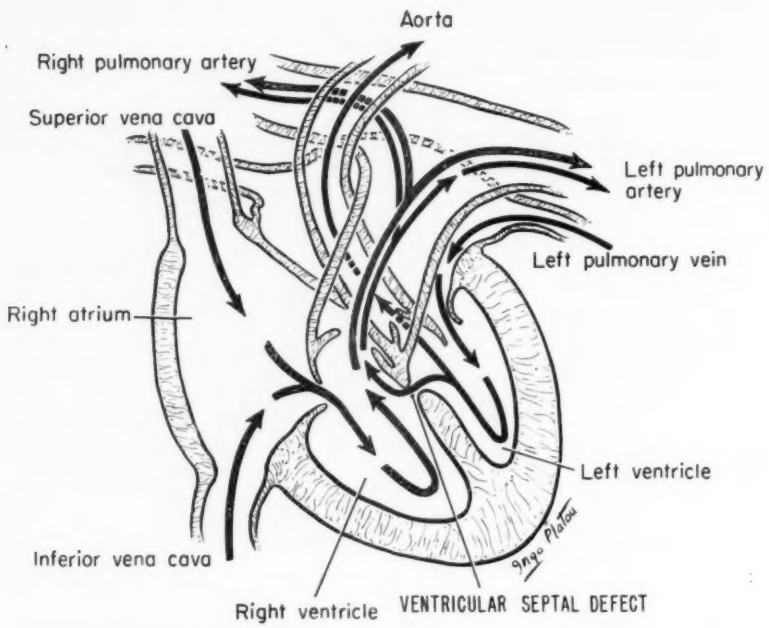
Patients with increased pulmonary arterial vasculature on the basis of left-to-right shunts (table 4) usually show, in addition to the increased vasculature, an enlarged pulmonary artery. This is true in all conditions in table 4 save those with corrected transposition.[2] Of common left-to-right shunts, patent ductus arteriosus usually demonstrates a large, vigorously pulsating aorta. In addition, there frequently is enlargement of the left atrium; often some enlargement of the left ventricle as well as of the right can be demonstrated. The others of the four common lesions in this group usual-

TABLE 3

INCIDENCE OF COMMON CONGENITAL HEART LESIONS (1,283 CASES)*

	PER CENT
Increased pulmonary vasculature	
Interventricular septal defect	22
Patent ductus arteriosus	12
Interatrial septal defect	11
Atrioventricularis communis	4
Total left-to-right shunt	49
Transposition of great vessels	6
Truncus arteriosus	3
Total admixture lesions	9
Normal pulmonary vasculature	
Coarctation of aorta	7
Aortic stenosis	3
Pulmonary stenosis	4
Subendocardial fibroelastosis	2
Decreased pulmonary vasculature	
Tetralogy of Fallot	12
Tricuspid atresia	3
All other lesions	13

*Abstracted freely from Gasul and Fell.[3] The percentages shown have relative significance only.



VENTRICULAR SEPTAL DEFECT

FIGURE 3.

ly present a small, relatively weakly pulsating aorta. In some cases of ventricular septal defect the aorta appears normal. Ventricular septal defect and atrioventricularis communis (A.V. canal) usually show an enlarged left atrium, and the left ventricle also may be enlarged. Children with atrial septal defect usually show pure right-sided enlargement and do not have enlargement of the left atrium.

The admixture lesions (table 5) as a rule show increased pulmonary arterial vasculature but with a flat pulmonary artery. Thus, they usually can be separated from the left-to-right shunt lesions, which show an enlarged pulmonary artery segment. This is due to the abnormal position of the great vessels which is characteristic of transposition, most cases of truncus arteriosus, single ventricle or cor biloculare (which usually are associated with transposed great vessels), and of tricuspid atresia with transposition of the great vessels.

TABLE 4

INCREASED PULMONARY ARTERIAL VASCULATURE; LEFT-TO-RIGHT SHUNT (ACYANOTIC)

Interatrial septal defect
Interventricular septal defect
Atrioventricularis communis
Patent ductus arteriosus
Partial anomalous pulmonary venous return
Aortic-pulmonic window
Ruptured sinus of Valsalva
Corrected transposition with left-to-right shunt
Lutembacher's syndrome
Coronary artery fistula

TABLE 5

INCREASED PULMONARY ARTERIAL VASCULATURE

A. *Admixture (cyanotic)*
Transposition of the great vessels
Truncus arteriosus
Single ventricle
Cor biloculare
Taussig-Bing anomaly
Total anomalous pulmonary venous return
Tricuspid atresia with transposition of the great vessels
B. *Shunt with marked pulmonary hypertension*
Reversing patent ductus arteriosus
"Eisenmenger complex"

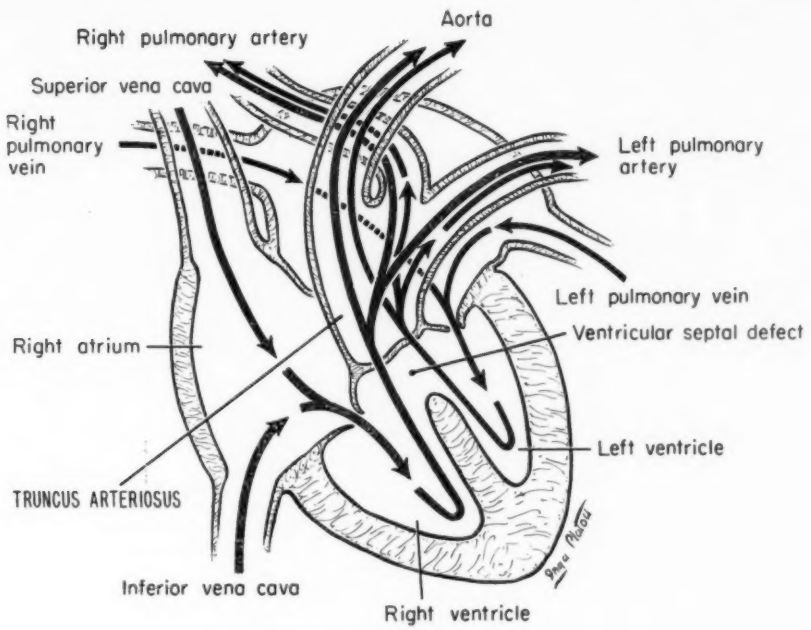


FIGURE 4.

In the relatively rare cases of Taussig-Bing anomaly and total anomalous pulmonary venous return, however, the pulmonary artery is seen along the left border of the heart, and it is enlarged. All these lesions belong in the cyanotic group.

Shunt lesions and pulmonary hypertension sufficient to create right-to-left shunts (table 5) are relatively rare in children. Their general characteristics are similar to those of the left-to-right shunts. An exception we have seen is primary pulmonary hypertension and patent foramen ovale in infants. This is discussed subsequently.

Patients demonstrating decreased pulmonary vasculature (table 6) have lesions associated with obstruction to the pulmonary outflow plus a defect permitting a shunt of blood from the right side of the heart to the left. The classic example is tetralogy of Fallot, where there usually is an obstruction to the flow of blood in the infundibulum of the right ventricle due to hypertrophy of the crista supraventricularis plus an interventricular septal defect. In some patients the obstruction is found at the pulmonary valve itself. In certain patients the obstruction is of moderate grade only, the right ventricular pressure is only modestly increased, and the shunt of blood through the interventricular septal defect is from left to right. These patients then may have increased pulmonary vasculature. The important feature here, it should be noted, is the degree of hypertension in the right ventricle. Since the ventricular septal defect is just beneath the aortic valve in most cases, the direction of the shunt depends on the relative pressure in the two ventricles, and the

TABLE 6

DECREASED PULMONARY ARTERIAL VASCULATURE

Tetralogy of Fallot
Tricuspid atresia
Trilogy of Fallot
"Pseudotruncus arteriosus"
Primary pulmonary hypertension with patent foramen ovale
Ebstein's anomaly (with atrial septal defect)

TABLE 7

NORMAL PULMONARY ARTERIAL VASCULATURE (ACYANOTIC)

Coarctation of aorta
Aortic stenosis
Subendocardial fibroelastosis
Congenital mitral stenosis
Cor triatriatum
Aortic ring
Pure pulmonic stenosis
Friedreich's ataxia heart disease
Congenital ventricular aneurysm
Anomalous origin of left coronary artery
Von Gierke's disease
Complete heart block
Cardiac tumor
Hypertensive heart disease
Metabolic heart disease
Marfan's disease

TABLE 8

SOME INDICATIONS FOR ANGIOCARDIOGRAPHY AND THORACIC AORTOGRAPHY

Angiocardiography
Congenital heart disease with decreased pulmonary vasculature
Congenital heart disease with increased pulmonary vasculature
Admixture type
Bidirectional shunts
Inability to enter the pulmonary artery at heart catheterization
Differential diagnosis between valvular and infundibular pulmonary stenosis
Anomalies of pulmonary vascular tree
Differential diagnosis between cardiac dilatation and pericardial effusion
Cardiac tumors
Certain pericardiac tumors
Thoracic aortography
Coarctation of the aorta
Patent ductus arteriosus
Aortic-pulmonic window
Differential diagnosis between aortic stenosis and aortic insufficiency
Ruptured aneurysm of sinus of Valsalva
Coronary artery fistula

aorta need not be, and in fact usually is not, "dextraposed" or in abnormal position. The aorta is, however, enlarged in patients with this disease in its cyanotic form.

About half of the patients with tetralogy of Fallot demonstrate no over-all cardiomegaly in their posteroanterior roentgenograms, although right ventricular enlargement is seen in the oblique and lateral views. In addition to the decreased pulmonary vasculature the pulmonary artery segment is flat or concave as a rule, with the rare exception of patients in whom there is valvular stenosis without an infundibular component and the occasional case associated with corrected transposition. There is a right aortic arch in about 25 per cent of these patients. The aorta invariably appears enlarged in cyanotic patients with this lesion.

Of the other lesions in this group, it should be noted that in tricuspid atresia there must be both a right-to-left shunt at the atrial level and a left-to-right shunt at the ventricular or ductus level in order for the circulation to be maintained.

Primary pulmonary hypertension with patent foramen ovale is of interest because the obstruction is in the pulmonary vessels themselves, which show thickening and narrowing. In infants with this disorder the pulmonary vasculature appears decreased in the x-ray.

Trilogy of Fallot is a lesion with pulmonary stenosis of the valvular type plus an interatrial septal defect with right-to-left shunt due to increased pressure on the right side of the heart. The roentgenogram usually shows decreased pulmonary vasculature, moderate to advanced cardiomegaly with right ventricular enlargement, frequently left atrial enlargement, and a moderately dilated pulmonary artery segment.

Ebstein's anomaly is an abnormality of the tricuspid valve with displacement of one or more of the valve leaflets from the valve ring and other defects of the valve leaflets resulting in anatomic incompetence and apparent physiologic stenosis of the valve. There is marked increase in the right atrial pressure, and in the presence of a patent foramen ovale there will be right-to-left shunt. These patients frequently present a characteristic roentgenographic appearance with a massively enlarged boxlike heart and with decreased pulmonary vasculature.

Patients with normal pulmonary arterial vasculature (table 7) represent a highly miscellaneous group, characterized, however, by

the fact that there is no shunt mechanism involved in the lesion. These patients can be further subdivided on radiologic grounds into those with a left-sided lesion such as coarctation of the aorta or aortic stenosis, those with a right-sided abnormality such as isolated pulmonary stenosis, and those with generalized lesions including certain rare metabolic conditions such as Von Gierke's disease.

Isolated pulmonary valvular stenosis requires some separate consideration. The appearance of this disorder on the roentgenogram is characterized by right ventricular enlargement and dilated pulmonary artery segment. In some cases of isolated pulmonic stenosis there is dilatation of the left branch of the pulmonary artery as well as the pulmonary trunk, the poststenotic dilatation being carried on into the left side; it may, therefore, be larger than the right branch. The peripheral pulmonary arterial vasculature is normal in the great majority of cases in children. While an occasional case may show decrease in the pulmonary vasculature, due to a decrease in circulating blood volume, this is a rare situation in the childhood age group. In most cases the presence of the cardiac findings mentioned, with an absolute decrease in the peripheral pulmonary vasculature, indicates the presence of the trilogy of Fallot, pulmonary stenosis plus an interatrial septal defect with right-to-left shunt.

Indications for Angiocardiography and Retrograde Aortography

Table 8 lists some, but by no means all, of the indications for angiocardiography and retrograde aortography. The first two indications are self-explanatory. In our experience there is a high correlation between inability to enter the pulmonary artery and corrected transposition; failure to enter the pulmonary artery is therefore considered an indication for angiocardiography. When the differential diagnosis between isolated valvular and infundibular stenosis cannot be established with certainty by other methods, angiocardiography —preferably by the selective method through a catheter placed in the right ventricle—is of great aid. Angiocardiography also is of value in anomalies of the pulmonary vascular tree.

Thoracic aortography is utilized mainly in the conditions listed. In cases in which precise diagnosis is firmly established by other methods the use of this technic is superfluous. But, in difficult or equivocal cases aortography usually is diagnostic, particularly in the first two conditions listed. In many of these conditions, conventional retrograde aortography with injection into the brachial artery will not be satisfactory, and injection preferably is made through a catheter placed in the ascending aorta.

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Current Concepts of Sexual Abnormalities

STANLEY NEWMAN,* VINCENT C. DiRAIMONDO† AND FELIX O. KOLB†

Tripler U. S. Army Hospital, Honolulu, and
University of California Medical Center, San Francisco

The gonads, germ cells, and internal and external genital systems are bipotential early in fetal life. Failure to develop in a manner which corresponds to the genetic sex usually results in gonadal or genital abnormalities. Recent progress has clarified the patterns of sexual development, and it is possible to diagnose and treat most of these abnormalities early in life.
Turner's syndrome, true hermaphroditism, Klinefelter's syndrome, and pseudohermaphroditism are discussed in relation to normal sexual development, which is categorically divided into six phases.

STANLEY NEWMAN

SEXUAL anomalies are not rare but frequently they are unrecognized or are diagnosed late in life when therapy is less satisfactory. Gonadal abnormalities have been confusing in the past because of lack of proper laboratory verification. Classifications were based mainly on clinical features, which can vary widely. The work of Jost[1] concerning gonadal influence on development of internal and external genitalia and that of Barr and associates[2] on the chromatin sex pattern have led to better understanding and a more accurate classification of sexual abnormalities. Detailed reviews by Grumbach and Barr,[3] Witschi and co-workers,[4] Greenblatt,[5] Greene[6] and others are available. We feel, however, that delineation of a working approach for the practicing physician would aid in the recognition and subsequent treatment of patients with these abnormalities.

The illustrations used in this presentation are diagrams outlining current concepts of normal gonadal development and of deviations which produce sexual abnormalities. In the central column of each, the undifferentiated structures appear. Increasing maleness is shown to the left, and increasing femaleness

*Major, M. C., United States Army; Chief, Radioisotope Clinic, Tripler U. S. Army Hospital, Honolulu, Hawaii.

†Metabolic Unit, University of California Medical Center, San Francisco, California.

VINCENT C. DI RAIMONDO

FELIX O. KOLB

to the right. In the extreme left and right columns are normal male and female structures, respectively. The other columns show partially differentiated structures or factors which influence the direction of the sexual development.

Normal Development of the Reproductive System

Knowledge available at present permits the division of developmental events leading to the final stage of genital formation into six phases, although these are not distinctly separable chronologically.

1. Genetic sex—Genetic sex is determined by the chromosomal pattern of the spermatozoon at the time of fertilization. Each ovum contains one X chromosome, but half of all spermatozoa contain an X and the other half a Y chromosome. When an ovum and a spermatozoon containing an X chromosome combine, a genetic female (XX) results, and a high percentage of the somatic cells contain a chromatin mass in the periphery of their nuclei (chromatin-positive cells) during intra-uterine as well as extra-uterine life. When a spermatozoon with a Y chromosome fertilizes an ovum, a genetic male (XY) results, and the chromatin mass is lacking in all but a small percentage of somatic cells. The chromatin sex pattern in both sexes is apparent even before gonadal formation occurs in the fetus.

2. Undifferentiated gonad (one to six weeks)—By the migration of the primordial germ cells into the primitive gonadal folds, the undifferentiated ("sexless") gonads come into existence. They consist of what has been called a cortex and a medulla, which are cell accumulations of different origin. Essential for this discussion is that the final gonads take their origin from *anlagen* which are sexually nonspecific, or ambisexual.

3. Differentiation of the gonad (seventh week)—Studies in the field of experimental embryology suggest that a factor as yet unidentified (evocator) stimulates the primitive gonad to develop in a direction corresponding to the genetic sex. As a result the cortex will form an ovary or the medulla a testis. The predominance of the differentiating portion of the gonad is associated with a regression of the opposite portion.

4. Development of the internal genital system (8 to 12 weeks)—The müllerian ducts originating from the urogenital ridge and the wolffian ducts from the mesonephros form the female and male internal genitals, respectively. Both ducts are present initially in the developing fetus and provide therewith the potentiality for development of the internal genitalia of either sex. Jost[1] demonstrated that castration of embryos before any sexual differentiation has begun results in development of the female internal and external genital system. This observation implies that the ovaries do not influence development of the müllerian ducts into a uterus, fallopian tubes and upper vagina or the associated retrogression of the wolffian ducts. On the other hand, in the male fetus the testis produces a local hormone factor which stimulates development of the wolffian duct into a vas deferens, epididymis and seminal vesicle, while simultaneously the structures of the müllerian duct disappear or fail to undergo further differentiation. The local factor is not testosterone or any other known androgen, and its effect is restricted to the same side only. Bilateral functioning fetal testes are therefore essential for formation of the normal male internal genital system.

5. Development of the external genital system (13 weeks to birth)—Differentiation of external genitalia involves changes in the urogenital sinus and genital tubercle, the *anlagen* of which are already present in the fifth week. Like the primitive gonads and genital ducts,

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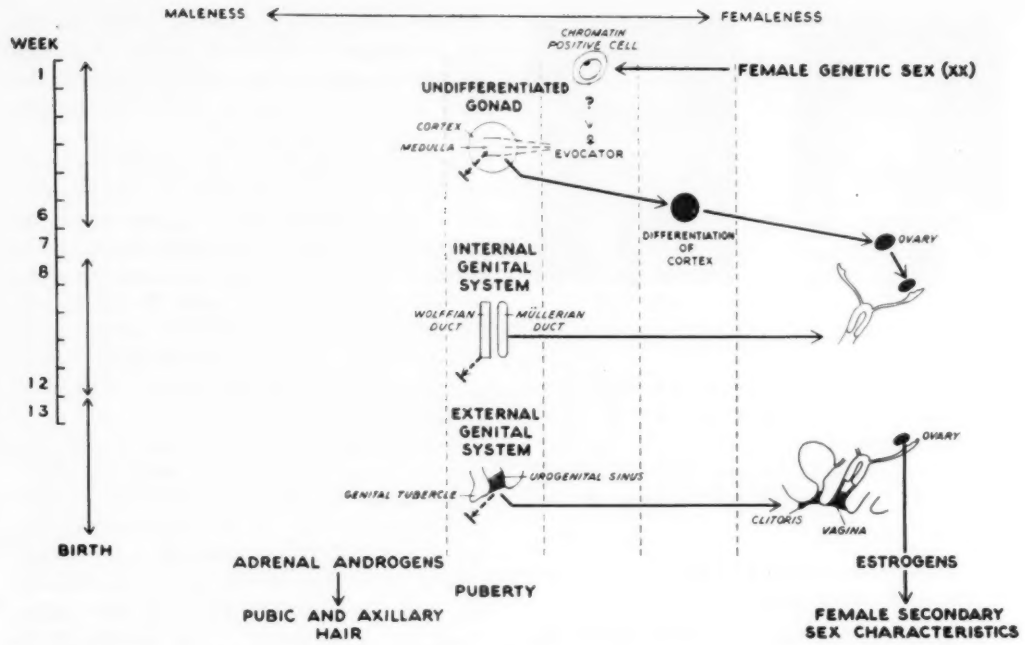

FIGURE 1. Normal female development. In this and the other illustrations, which are diagrams outlining current concepts of normal gonadal development and deviations in pattern which produce sexual abnormalities, the undifferentiated structures appear in the central column. Increasing maleness is shown to the left and increasing femaleness to the right. In the extreme left and right columns are normal male and female structures, respectively. Other columns represent partially differentiated structures or factors influencing the direction of sexual development.

the external genital system is initially ambisexual. Although differentiation of external genitalia begins shortly after the internal genitals have formed, it can be influenced by hormonal factors up to the time of birth. The female external genitalia develop even in the absence of any ovarian influence. The lower vagina and clitoris result from persistence of the urogenital sinus and failure of genital tubercle enlargement, respectively. In the male embryo, testicular androgens cause closure of the urogenital sinus, fusion of the labioscrotal folds, enlargement of the genital tubercle, and descent of the testes by the seventh month. Leydig's cells, prominent during this stage of development, probably are the source of fetal androgens.

6. Puberty.—From birth to puberty, significant sexual changes normally do not occur. In the adolescent female, ovarian hormones cause enlargement of the breasts, uterine growth, development of external genitalia, menstruation, and so on, but adrenal androgens probably influence the growth of pubic and axillary hair. Testicular androgens, especially testosterone, are responsible for the male secondary sex characteristics that appear at puberty.

Normal Female Development

Figure 1 is a diagrammatic outline of current concepts of normal female development. At the time of fertilization, an X chromosome in both the spermatozoon and the ovum results in female genetic sex (XX). This is reflected by the presence of chromatin-positive somatic cells as fetal development occurs. At six weeks the undifferentiated gonad, containing a cortex, a medulla and germ cells, is influenced by an unidentified factor to develop in a female direction. The gonadal cortex differentiates and medullary development is sup-

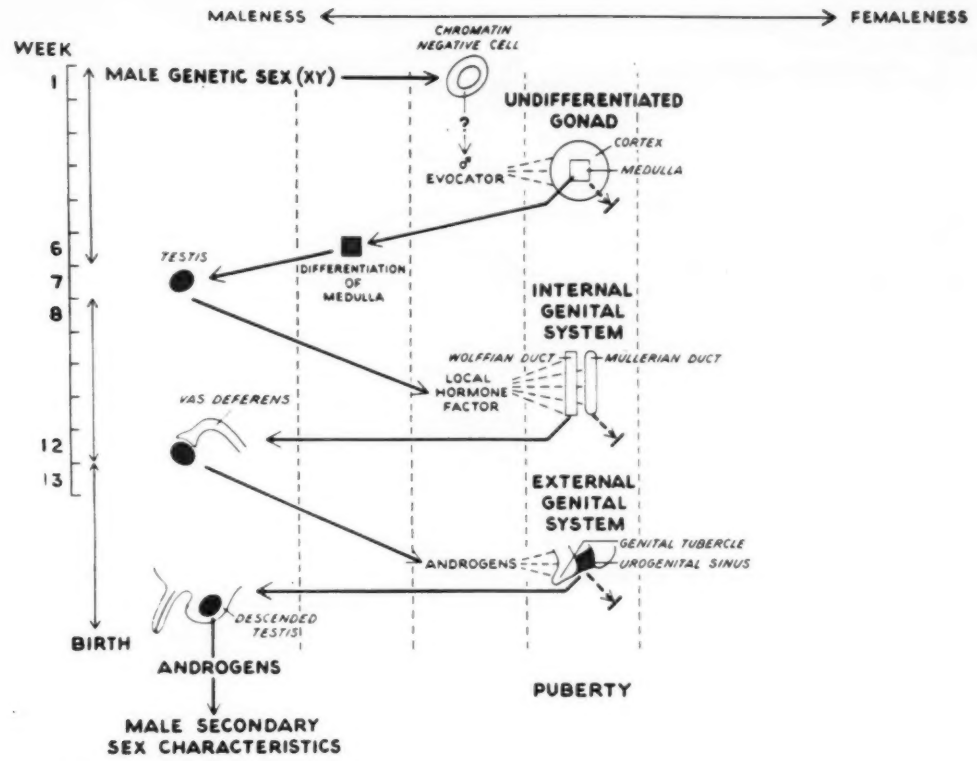

FIGURE 2. Normal male development.

pressed, resulting in formation of the fetal ovary at seven weeks. From the eighth to the twelfth week the müllerian ducts form the female internal genitalia and the wolffian ducts disappear. Thereafter the urogenital sinus is transformed into the lower vagina and labia, while the genital tubercle remains small. Development of the internal and external genital systems is independent of ovarian influence, whereas evolution of such secondary sex characteristics as enlargement of the breasts and menstruation at puberty is a result of hormonal secretion from the ovary.

Normal Male Development

The combination of an ovum and a spermatozoon carrying a Y chromosome at fertilization results in a male genetic sex, which is reflected by chromatin-negative somatic cells (figure 2). At six weeks, differentiation of the medulla in the primitive gonad forms a testis, and further development of its cortical portion is suppressed. The fetal testis secretes a local factor which causes development of the wolffian duct and suppression of the müllerian duct on that side. At 8 to 12 weeks the wolffian duct forms the vas deferens, seminal vesicle and epididymis. After 13 weeks the genital tubercle enlarges, the urogenital sinus closes, the labioscrotal folds fuse to form the scrotum, and the testes descend. These changes are not completed until late in fetal life. Presumably, testicular androgens are responsible for the masculinization of the external genitalia. At puberty, testicular androgens cause the male secondary sex characteristics.

Abnormal Development

Figures 3 to 7 summarize the variations from the normal pattern which are responsible

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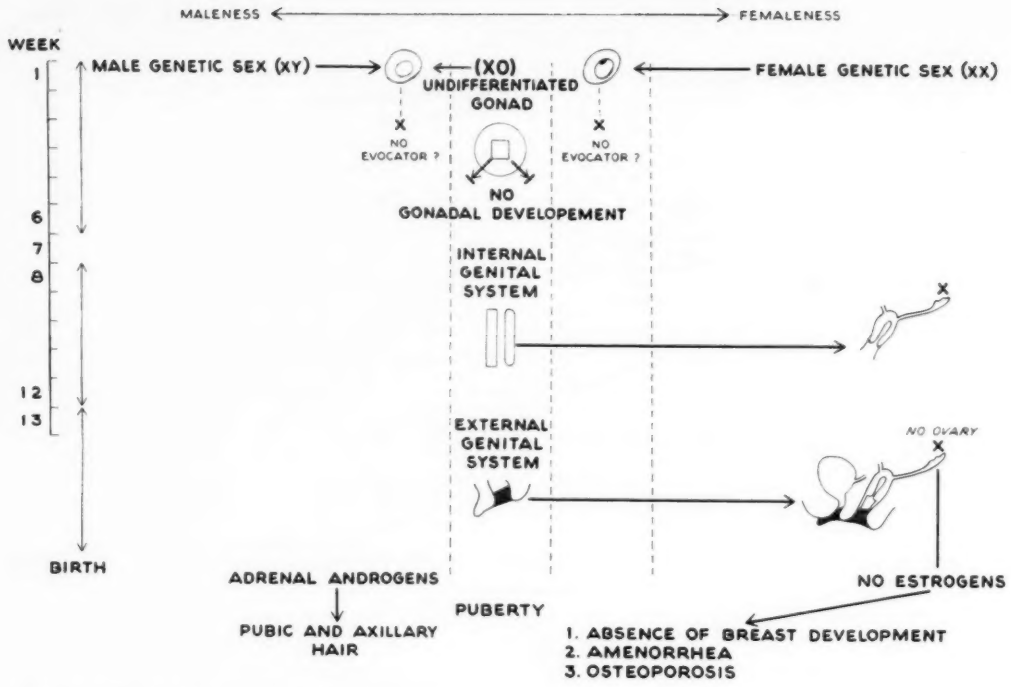

FIGURE 3. Gonadal dysgenesis (Turner's syndrome).

for some of the better-understood sexual abnormalities.

When the gonad and internal and external genitalia fail to develop in a completely male direction with disappearance of the female *anlage*, or when they fail to develop in a completely female direction with regression of the male *anlage*, sexual anomalies occur. These potentially may arise during any stage of development from early fetal life to adulthood.

1. Genetic sex—New technical developments which permit direct examination of chromosomes in somatic cells have demonstrated an extra chromosome (XXY) in the Klinefelter syndrome[7] and a subnormal number (XO) in Turner's syndrome.[8] Whether or not there are recognizable alterations in somatic chromosomes in other gonadal abnormalities will require further study. The chromatin sex pattern is not altered by aberrant sexual development or by the administration of hormones.

2. Undifferentiated gonads—Disturbance of the primitive gonad, by lack of either cortex or medulla, or by disproportion of the two parts, is probably responsible for some of the gonadal anomalies, but present knowledge does not permit us to attribute accurately any of the known clinical entities to a failure of normal development at this stage.

3. Differentiation of the gonad—This is the first stage wherein developmental defects result in clinically apparent abnormalities. When the gonads fail to differentiate in a manner corresponding to the genetic sex, either the gonad was unable to develop normally or an abnormal evocator must have been present. Patients with gonadal agenesis (gonadal dysgenesis) (figure 3) have female genital organs but only gonadal streaks where ovaries are normally present. When other congenital anomalies are associated with the condition, such as webbing of the neck, dwarfism and coarctation of the aorta, it is better known as

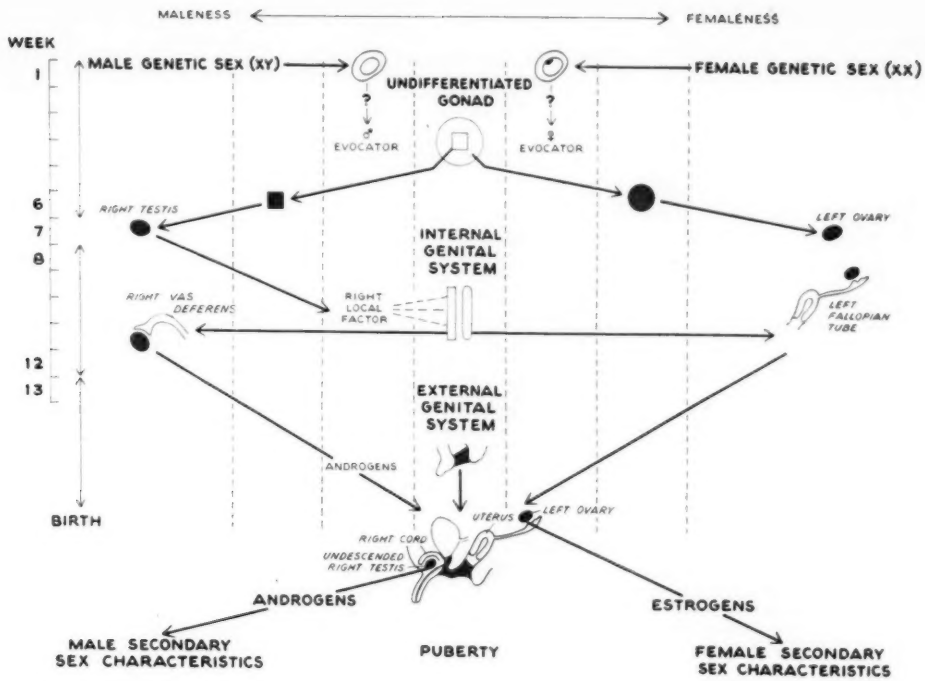

FIGURE 4. True hermaphroditism.

Turner's syndrome. Absence of a gonadal influence during fetal development is associated with formation of female internal and external genitals. Because most of these patients have been found to be genetic males and direct examination of the chromosomes has shown an XO pattern,[8] determination of the chromosomal sex pattern is of great value in diagnosing these cases early in life. Although normal-appearing female genitalia are present during childhood, the absence of functioning ovaries prevents spontaneous growth of breast tissue and the occurrence of menstruation at puberty. Some pubic and axillary hair may result from influence of androgens secreted by the adrenals or by clumps of cells resembling Leydig's cells in the gonadal streaks.

In true hermaphroditism something abnormal also must happen during the period of gonadal differentiation, since it appears that either the cortex or the medulla fails to express its dominance and to cause the other to disappear. Consequently both ovarian tissue and testicular tissue develop in the same person. The type illustrated in figure 4 has an ovary on one side and a testis on the other. These patients can be genetically male or female, although the majority have been found to be chromatin-positive. In the example that is shown in the diagram, a testis originating from the medulla of one undifferentiated gonad emits a local factor which stimulates the genital system on that side to form a vas deferens, a seminal vesicle and epididymis but has no influence on the internal genital system on the other side, where the organs derived from the müllerian duct (tube, uterus, upper vagina) continue their development. The external genital system usually is a mixture of male and female characteristics with a predominance of one or the other, probably depending on the amount of androgens the fetal testis secretes. Frequently the genitalia appear ambiguous, with some enlarge-

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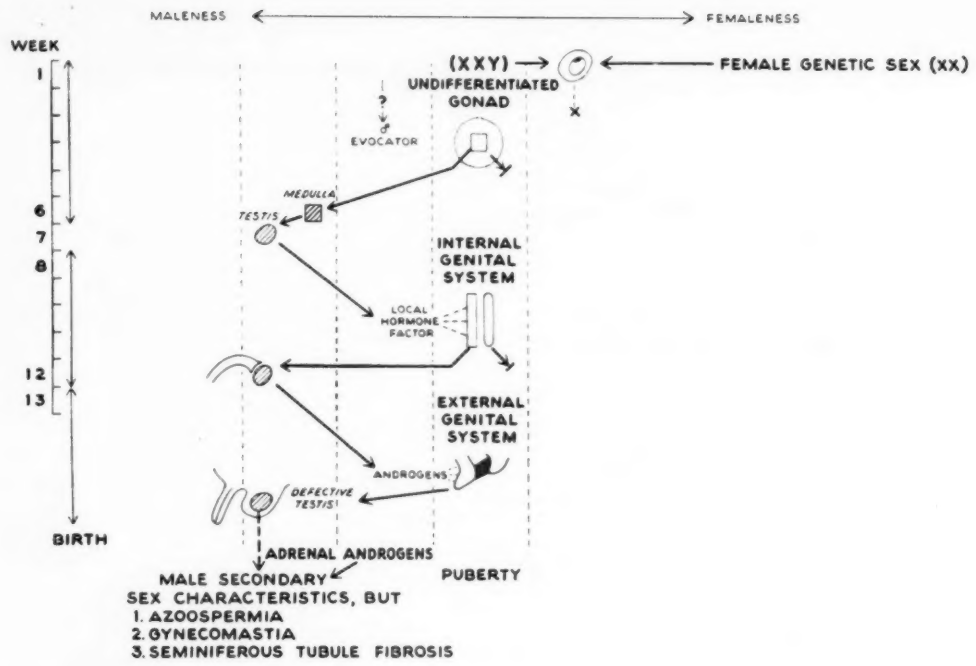

FIGURE 5. Klinefelter's syndrome.

ment of the genital tubercle, incomplete closure of the urogenital sinus, and undescended testis. During puberty, either the ovary will predominate, secrete estrogens and produce secondary female characteristics, or testicular androgens will result in masculinization.

Patients with Klinefelter's syndrome (seminiferous tubular dysgenesis) (figure 5) are infertile and have small testes, gynecomastia, and fibrosis or hyalinization of the seminiferous tubules. They are most frequently of the female genetic sex and have shown an XXY pattern.[7] Evidently the cortex of the undifferentiated gonad fails to develop, either because of a defective undifferentiated gonad which contains a reduced number of germinal elements or as a result of an abnormal evocator. One may consider a true hermaphrodite to stem from a partial suppression of cortical development in a genetic female, and Klinefelter's syndrome to stem from a complete suppression.[3] The medulla persists bilaterally, forming testes which are not completely normal. The testes do produce the factors necessary for masculinization of the internal and external genitalia and descend normally, resulting in a normal male appearance at birth and during childhood. During puberty, enough androgens usually are produced by interstitial cells of the testes and by the adrenals to result in male secondary sex characteristics, except for small testes which contain fibrosed or hyalinized tubules. The Leydig cells are amply represented, but whether there is truly a hyperplasia of these cells or only an apparent increase in number as a result of shrinkage of the tubules has not been determined. Spermatogenesis, although somewhat scanty, can be observed in the tubules. Even though only a few spermatozoa are found, Klinefelter's syndrome demonstrates nature's ability to produce them in a genetic female, indicating the potential nature of the germ cells to develop in either a male or a female direction.[5] Wheth-

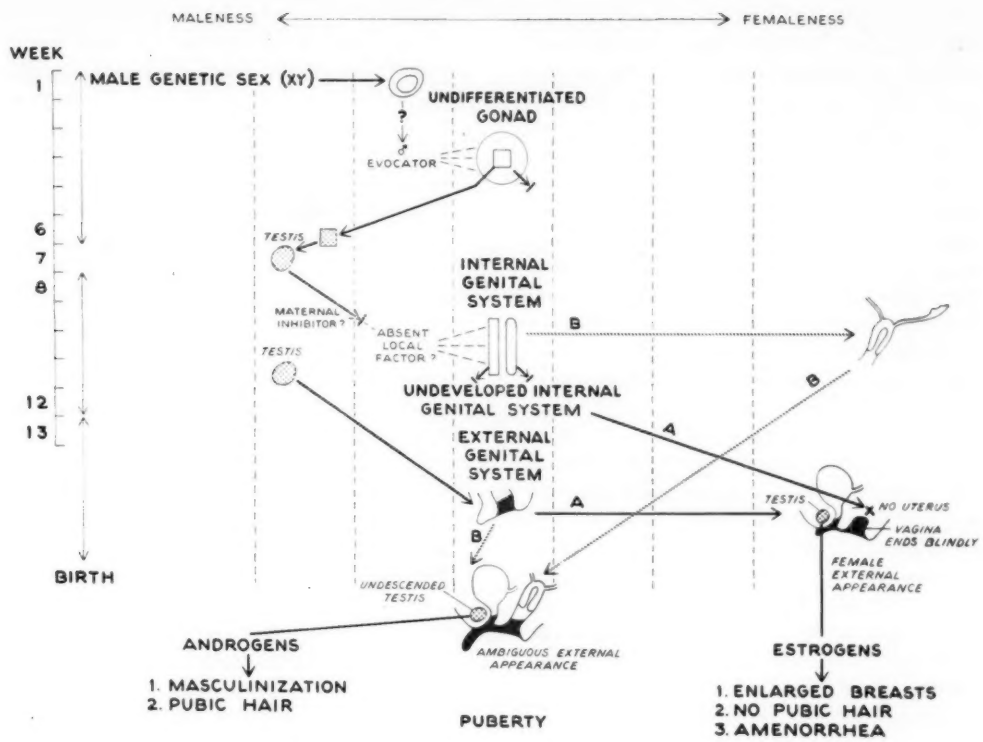

FIGURE 6. Male pseudohermaphroditism.

er the gynecomastia in Klinefelter's syndrome results from an increased secretion of estrogens or from production of an abnormal testicular steroid is not known.

4. Development of the internal genital system—The testicular influence on internal genital development is limited to the same side. Consequently the true hermaphrodite with a unilateral testis (figure 4) forms male internal organs on that side only; on the other side, female genitalia may form.

Absence of a functioning fetal testis is associated with bilateral differentiation of female internal organs. As a result, patients with gonadal agenesis (figure 3) with no gonads, as well as female pseudohermaphrodites (figure 7) with normal ovaries, develop female genital organs.

Although testes are present in male pseudohermaphrodites, either they are inherently defective or a maternal inhibitor (figure 6) prevents their normal influence on sexual development. (This appears to be an inherited disorder in which an abnormal gene is transmitted by a supposedly healthy mother to half of her genetically male children.) In some instances (figure 6, type A) neither the wolffian nor the müllerian ducts develop but the external genitalia have a normal female appearance at birth. However, the lower vagina ends blindly because of failure of the uterus and upper vagina to develop. The defective undescended testes frequently can be palpated in the inguinal canals. At puberty these testes may secrete estrogens which cause breast development. Amenorrhea results from absence of a uterus and therefore is not responsive to estrogen therapy. One-third of such patients lack pubic hair because of unresponsiveness of the hair follicles to hormones. In other

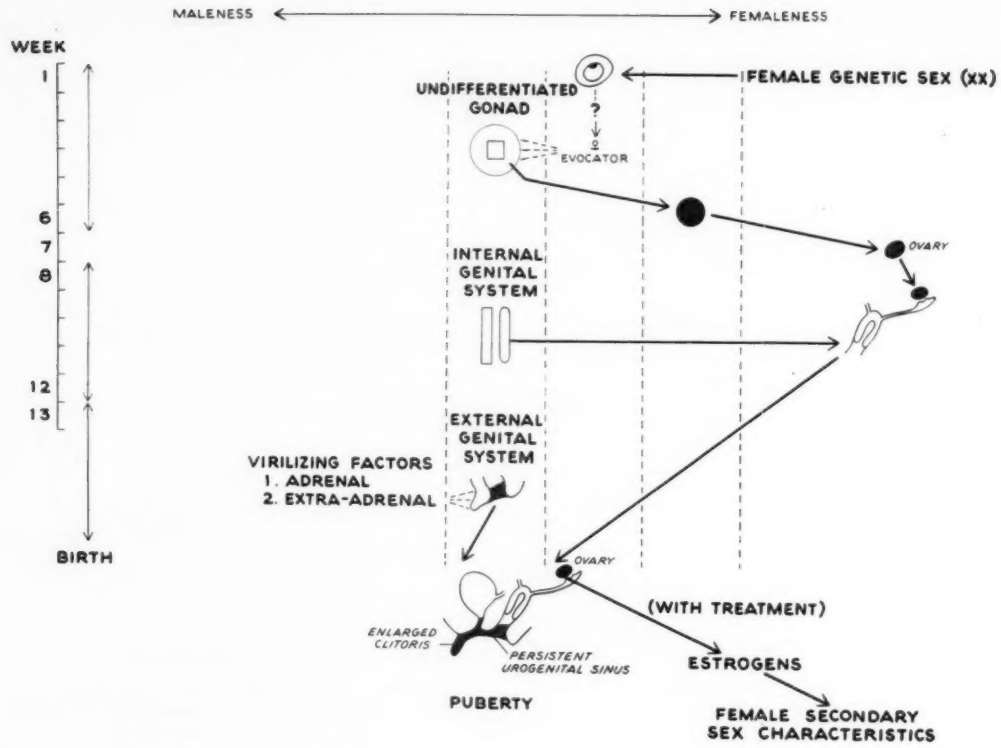

FIGURE 7. Female pseudohermaphroditism.

cases with partial or complete development of müllerian ducts (figure 6, type B) a uterus and fallopian tubes form but fetal testicular androgens cause partial masculinization and an ambiguous appearance of the external genitalia. At puberty these testes may cause either masculinization or feminization.

5. Development of the external genital system—Just as a local testicular factor influences internal genital development, so does masculinization or feminization of the external genitals depend on the presence or absence of testicular androgens. In Klinefelter's syndrome the testes cause complete male development of the external as well as internal organs. Some true hermaphrodites and male pseudohermaphrodites (type B) have ambiguous external genitalia because of partial but inadequate testicular androgenic influence. Other male pseudohermaphrodites (type A) and patients with Turner's syndrome who do not have testicular androgens have female external genitalia.

Until the external genitalia enter the latest stage of development the female pseudohermaphrodite (figure 7) has had normal development of ovaries and internal genitalia. During the last half of fetal life, however, a virilizing factor, usually of adrenal origin, causes a variable degree of clitoral enlargement and closure of the labial folds. This condition has also been reported following administration of progesteronelike compounds or androgens to the mother.[9] The virilizing factors of maternal origin no longer persist after birth, in contrast to those of fetal origin which usually continue. At birth the clitoral enlargement and fusion of the labioscrotal folds frequently result in a mistaken diagnosis of a cryptorchid male. Many surgical proce-

dures to correct hypospadias and cryptorchism may be performed before the true nature of the disorder is discovered. In cases resulting from virilizing adrenal hyperplasia, androgenicity may progress, causing excessive growth and pseudoprecocious puberty in childhood or, in milder cases, hirsutism and inhibition of normal ovarian function in women.

6. Puberty—Except in female pseudohermaphroditism, little change occurs in sexual development between birth and puberty. At puberty, some of the sexual abnormalities may become more marked by the lack of development of secondary sex characteristics or by development in an unexpected direction. The breasts may not develop and amenorrhea persists in gonadal agenesis because of absent gonads. However, some pubic and axillary hair grows under the influence of androgens from the adrenal gland or Leydig's cells in the gonadal streaks. The true hermaphrodite and the male pseudohermaphrodite may become either feminized or masculinized. Masculinization occurs at puberty in Klinefelter's syndrome but is associated with azoospermia, gynecomastia and, frequently, a eunuchoid habitus. The female pseudohermaphrodite may have enough adrenal androgens during childhood to cause rapid growth and progressive virilization, or an abnormality may become apparent only after puberty when excessive androgens interfere with normal ovarian function by inhibition of pituitary gonadotropins. With adequate treatment, normal growth occurs during childhood and ovarian function produces feminine development after puberty.

Clinical Characteristics

Although gonadal abnormalities should be suspected in any patient with malformation of the external genitalia, they are also associated with normal-appearing male genitals (Klinefelter's syndrome) or female genitals (gonadal dysgenesis). Other congenital anomalies such as webbing of the neck and coarctation of the aorta frequently are present in Turner's syndrome, and Klinefelter's syndrome has a relatively high incidence in males with mental retardation. When other members of the family have similar genital anomalies there is an increased likelihood that a gonadal abnormality is present. Dwarfism is common in Turner's syndrome, rapid growth is common in virilizing adrenal hyperplasia, and eunuchoid habitus is common in Klinefelter's syndrome. Precocious virilization is relatively frequent in adrenal hyperplasia. Gonadal agenesis is associated with absence of female sexual development at puberty. Seminiferous tubular dysgenesis may be manifested only by infertility, but usually the testes are small and there is some degree of gynecomastia.

Careful genital examination may be of great value in clarifying the nature of a developmental anomaly. In gonadal dysgenesis a uterus but no ovaries can be palpated. In male pseudohermaphroditism with similarly normal-appearing female external genitalia (type A) the vagina ends blindly, a uterus is not present, and the gonads usually are palpable in the inguinal canals. After puberty, 30 per cent of such persons lack pubic hair due to insensitivity of the hair follicles. In the female pseudohermaphrodite with virilized external genitalia, careful internal examination will reveal the presence of a uterus and ovaries; genetic females with Klinefelter's syndrome have normally formed male internal and external genitalia. The true hermaphrodite may have male or female internal or external genital development.

Laboratory Studies

Simple laboratory tests frequently will indicate the need for further exploration or treatment. The chromatin sex pattern should be determined in any infant whose external genitalia are malformed or when other members of the family have gonadal abnormalities. When the chromatin pattern does not correspond to the genital type of development, further investigation is indicated. In virilizing adrenal hyperplasia the production of hydrocortisone is impaired and consequently the adrenals secrete excessive amounts of other hormones, including androgens, which are responsible for the genital abnormalities. Urinary levels of 17-ketosteroids and pregnanetriol usually are elevated. With corticotropin

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stimulation, the increase in urinary 17-hydroxycorticoid output is less than normal, while the 17-ketosteroids and pregnanetriol may be markedly elevated.

After puberty, Turner's syndrome and Klinefelter's syndrome are associated with abnormally high excretion of urinary gonadotropins. Azoospermia or marked oligospermia is found in Klinefelter's syndrome. In all conditions except virilizing adrenal hyperplasia, the specific diagnosis of a sexual abnormality is made by surgical exploration and histologic examination of the gonads.

Treatment

Therapy should be directed toward maintenance of gonadal function, ability to reproduce, and maintenance of psychic stability. When a diagnosis of gonadal abnormality is made in early infancy, the "social" sex should be governed by the nature of the gonadal tissue and genetic sex. The infant female pseudohermaphrodite with adrenal hyperplasia, having normal ovaries and virilized external genitalia, is preferably reared as a girl with the aid of early plastic repair of the external genitalia and corticosteroid therapy. Hydrocortisone or one of the newer steroids will reduce the excessive output of androgens, allowing normal growth during childhood and normal ovarian function at puberty. Normal female secondary sex characteristics will develop, including fertility, which would not be possible if the child were reared as a male, even though androgens can produce a significant amount of virilization. If the child already has been reared as a male, one should consider changing the "social" sex only after careful evaluation, preferably by an experienced psychiatrist. In most instances it is psychologically less traumatic to continue life as a male. One can avoid this situation in the future by determining the chromatin sex pattern early in life. With institution of hydrocortisone therapy, oophorectomy may be necessary to prevent feminization after puberty in patients who have been raised as males. Women who manifest only degrees of virilization and impaired ovarian function will respond well to corticosteroid therapy alone.

Estrogens produce satisfactory breast development and menstruation in patients with Turner's syndrome. Although many patients with Klinefelter's syndrome do not require androgens, this therapy helps those who are eunuchoid. Gynecomastia, if disturbing enough, is best treated by plastic surgery.

Almost all male pseudohermaphrodites have gross morphologic abnormalities of the testes, and a high incidence of malignant tumors in such patients is recognized.[10] In type A, in which genitalia are feminine in appearance and the testes secrete estrogens at puberty, one may permit puberty to take place spontaneously and, after adequate sexual development, remove the testes and initiate estrogen therapy. In type B, one cannot predict whether feminization or masculinization is likely to occur at puberty, and therefore it may be advisable to remove the gonads during childhood and administer estrogens or androgens at the time of puberty and thereafter. Treatment of the true hermaphrodite depends on the nature of the genital and gonadal tissue, the patient's age, and the sexual status imposed on him.

Summary and Conclusions

The gonads, germ cells, and internal and external genital systems are all bipotential, having the ability to develop in a female or a male direction early in fetal life. Development usually corresponds with the genetic sex; failure in this sense usually results in gonadal or genital abnormalities. Recent advances have made it possible to diagnose and treat most of these abnormalities early in the patient's life. Progression of symptoms is thereby avoided, the child is not mistakenly reared as a member of the opposite sex, and anatomic abnormalities can be corrected before serious psychologic trauma occurs. Recent progress has clarified the patterns of sexual development, but we must look to the future for isolation of factors which control the direction of gonadal and genital formation.

ACKNOWLEDGMENT

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Postgraduate Clinical NOTES

136. GOUT

Gout is a genetically conditioned disorder of uric acid metabolism characterized by hyperuricemia, deposition of urate crystals in the tissues and acute or chronic arthritis. The exact incidence of gout is not known because many persons with the inherited trait, probably the majority, live normal spans of life without developing manifestations. Asymptomatic hyperuricemia, according to estimates, is present in about 25 per cent of the relatives of patients with gouty arthritis. The metabolic abnormality is said to be transmitted by a single dominant autosomal gene which has a penetration of about 46 per cent in the heterozygous male and 12 per cent or less in the female.

The best-known clinical manifestation is gouty arthritis, which at first is acute, explosive and recurrent, and later tends to become chronic. It is less common than certain other forms of joint disease, but is by no means rare and accounts for about 5 per cent of diagnoses made among patients who attend clinics for arthritis. It has an overwhelming predilection for males: At least 95 per cent of cases occur in men and the burden of proof lies with the physician who makes a diagnosis of gouty arthritis in a woman. The disease does not exempt any race or social level, though its manifestations may be more prone to develop among men financially able to indulge freely in the provocatives of acute seizures.

E. W. Boland, Gout and gouty arthritis, *World-Wide Abstracts of General Medicine*, January 1960, pp. 11-17

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SYMPOSIUM

Resistant Staphylococcal Infections

EDGAR J. POTH,[1] MARK H. LEPPER[2]
AND MILES B. SMITH[3]

Are staphylococcal infections more frequent now than they were in the preantibiotic era? How have antibiotics influenced their occurrence? Is there evidence that strains of coagulase-positive staphylococci vary in virulence? What is "a dangerous carrier"? What is the role of the asymptomatic nasal carrier? What are the problems of eradication of the carrier state?

These questions are discussed on the basis of recent experiences in hospitals with problems in the control of resistant staphylococcal infections.

DR. EDGAR J. POTH (Moderator): The purpose of this panel discussion is to answer as many questions relating to resistant staphylococcal infections as we can, as accurately as we can. Dr. Smith, are staphylococcal infections more frequent today than they were 20 years ago?

DR. MILES B. SMITH: There is really no clearly defined evidence that they are, if one excludes the more dramatic incidents such as the acute epidemics, the newspaper stories about nurseries wiped out by virulent staphylococci, and the obstetric complications. There is still some argument among authorities about the over-all increase in sepsis that is presumed to exist, and when one considers the facts there is some doubt that in well-regulated, thoroughly disciplined, long-term surgical services there has been any real change. However, in my personal experience, in the few months since the correspondence about this meeting was begun there has been a rise in the incidence of wound infection from 4.3 to 9.8 per cent on our 317 bed service and a change in phage pattern of virulent staphylococci from a 7 per cent to a 44 per cent incidence of phage type 80-81.

DR. POTH: What constitutes a postoperative wound infection?

DR. SMITH: Certainly the argument about the importance of this will go on for the next thousand years, but the appearance of any sign

[1]Professor of Surgery, The University of Texas Medical Branch, Galveston, Texas.

[2]Professor of Preventive Medicine and Head of the Department, University of Illinois College of Medicine, Chicago, Illinois.

[3]Associate Professor of Surgery, Marquette University School of Medicine, Milwaukee; Chief, Surgical Service, Veterans Administration Center, Wood, Wisconsin.

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EDGAR J. POTH

MARK H. LEPPER

MILES B. SMITH

of suppurative clinical infection—swelling, purulent drainage, even minute—about a suture constitutes a wound infection, no matter how superficial or how trivial it may be.

I have some statistical data relating to this question of an increase of staphylococcal infection from two major hospitals in Massachusetts. They represent a 21 year study at Massachusetts General Hospital and a nine year study at Massachusetts Memorial Hospital, right across town, and the findings do not agree.

At Massachusetts General Hospital, the average incidence of wound infection due to all bacteria in a series of more than 3000 herniorrhaphies over a 21 year period was 5 per cent. Barnes and associates, who presented these figures, consider that the findings indicate that there has not been a significant change in the incidence of infection in 21 years in cases of inguinal hernia treated surgically. At the same hospital over a 21 year period the over-all rate of wound infection or sepsis in more than 6000 hysterectomies was only 3.2 per cent, and this, they say, has not varied significantly in 21 years. Now, many people would not boast about rates such as these for wound infections in a carefully controlled academic surgical service, so perhaps this is why there has not been a change; the incidence has never been low enough.

Across town at Massachusetts Memorial Hospital, Chester Howe reports that in his nine year evaluation the over-all rate of infection in clean wounds—and that is what we are talking about—has slowly and steadily risen. This, I think, is the general experience. It is like being on a small coral island with the tide rising; a few hospitals have been washed away by huge waves, but we are all watching the water creep up.

Why has the rate been rising? Even the more experienced surgeons, whose teaching responsibility enforces rigid discipline in the operating room, may have fallen into the antibiotic laxity common today, but certainly the resident has had more wound infection than could ever be considered acceptable. The highest level of wound infections was found among the resident staff or house physician cases, and the lowest among private patients.

DR. POTH: Are you sure that in this analysis the residents were not getting the poor-risk patients, the elderly ones whose financial status and general condition were less favorable? The residents' infection rate may really not have been higher, and may not have been as high as that of the regular staff, if they had the same type of patients.

DR. SMITH: I am sure that what you have just said explains about half of the difference in incidence, but these are clean cases, and no matter how many excuses we make for ourselves the reason stands. There must be a break in technic for such a dramatic rise to have occurred in nine years even among resident-type cases.

DR. POTH: What organisms were cultured? Is there evidence that these infections were due to coagulase-positive, resistant staphylococci, or do these figures indicate an over-all letdown in aseptic technic?

DR. SMITH: The data include all types of bacteria; there were increases in infections due to coliform organisms, nonpathogenic staphylococci, and coagulase-positive organisms. However, in my own experience the increase has been almost entirely in coagulase-positive, antibiotic-resistant staphylococci, and in the phage type 80-81.

DR. POTH: I believe that operating-room infections receive too much emphasis. In the

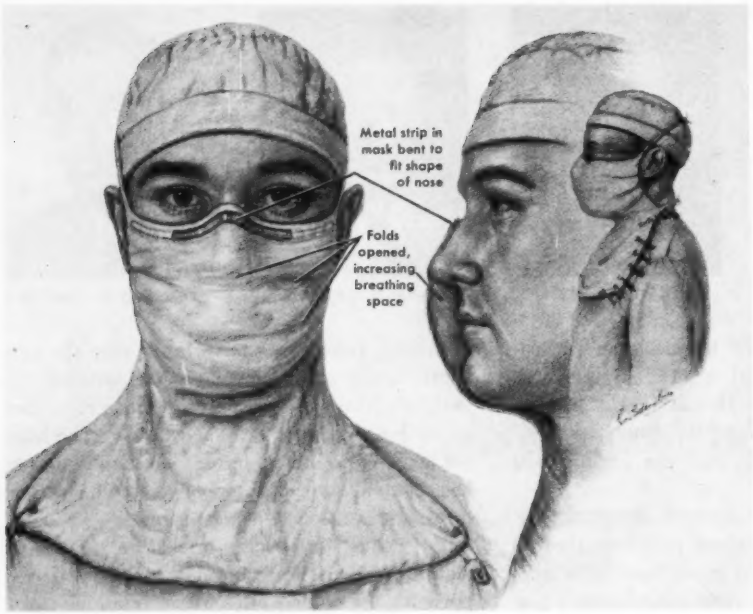


FIGURE 1. General design of the bib-mask and the manner in which it is worn. The upper tie is made sufficiently secure to give the tightness desired over the nose by the aluminum strip which is formed to fit the conformity of the nose and face. The lower tie is loosely secured. The corners of the mask are attached to the shirt by safety pins to keep it in position underneath the operating gown.

first place they should not occur except as accidents—and they will occur as accidents from time to time because there are bound to be breaks in technic; somebody, something fails, and an infection occurs. But this should not occur due to a poor approach, a letdown in asepsis. In the past few years at the hospital where I have worked, we have recognized the fact that we have had staphylococcal infections. We have had several epidemics, particularly in the nursery. On two occasions we have had outbreaks, and by pulling ourselves up by the bootstraps, so to speak—by cleaning up the place, controlling occupancy and eliminating carriers—we have straightened out the situation. However, as I said before, I think we put entirely too much emphasis on operating-room infections; they should be practically nonexistent if we are doing a proper job.

At our hospital we have two general surgical services which are completely parallel and which take alternate cases. Residents rotate from one service to the other every four months, and both services have the same nurses. During the past year, one of these services has had numerous coagulase-positive, resistant staphylococcal infections, while the other service has not had a single infection. The infections which occurred on the one service were not superficial but were deep infections; they must have been operating-room infections. In the operating room, one of these surgical services uses powder on gloves, and the other does not. One of the groups shaves the operative field the night before; the other shaves the operative field in continuity with the operative procedure. I believe that shaving the operative field hours prior to operation is probably one of the biggest breaks in asepsis. Almost all of us have been guilty of doing this for many years. We shave the operative field some hours before the patient is brought to the operating room. There are numerous small nicks, which may not be visible. They become contaminated, and by the time the patient reaches the operating room they are somewhat infected. Since we have in our hospital community some highly virulent organisms that are difficult to control, we get a high incidence of infection. We are asking for it.

Another difference between the two surgical

services at our hospital is that one uses a certain type of mask. The mask illustrated in figure 1 was developed 20 years ago. It is used on one service and not on the other. It is quite thick and closely woven. It fits loosely. A bib is attached which goes under the operating gown, so that the exfoliative particles from the face are carried under the gown and do not rain down into the wound. These large particles are most likely to cause infection, not the small particles which rise in the air stream if there is an upward current.

Still another difference is that on one service iodine (Betadine) is used in the preparation of the skin of the patient.

The occurrence of wound infections on one of these surgical services and their absence on the other is not merely a matter of difference in the ability and technic of the personnel. The personnel are the same on both services. The residents do not all begin their four month rotation on one service and then go to the other, so the reason cannot be that they have had a little more experience in the service without wound infections. These infections must occur in the operating room. I think that simple technical procedures will prevent infection here, and we are failing in proper asepsis when deep wound infections occur.

DR. SMITH: There is no question about it; you are completely right.

DR. MARK H. LEPPER: Certainly wound infections are an important part of this problem of resistant staphylococcal infections, but they are not the entire problem. I would like to speak from a medical man's point of view. I have participated in several panel discussions on this subject in the past eight or nine years, from the time when it was a relatively unpopular subject to the present, when it is quite popular. On these panels I have met several people who one year have said it is no real problem and the next year have reversed their position after they have had a few patients die from enterocolitis or some disease like that.

I think we have to say that based on the over-all autopsy results in all types of cases there are more staphylococcal infections among patients with terminal pneumonias, patients dying of cardiac disease, and some of the advanced surgical patients whose wounds are not as clean as those chosen for the studies just reported; in these situations, in all probability, staphylococcal infection has increased. Three factors make it difficult to say this with certainty. First, I think we are more sure of ourselves these days when we diagnose a staphylococcal infection than we were in the late 1930s when we had more streptococcal disease and more pneumococcal disease. For example, in terminal pneumonia, if pneumococci and staphylococci were present one would say, "Aha! It is a *Pneumococcus*." We are reasonably sure now it is the *Staphylococcus* in many of these patients. Secondly, the patients we see are much different. I think the repartee about the type of patient the resident gets is all-important in the total picture. We have patients who are living on steroids to keep alive; the steroids also allow more serious pathologic situations to exist at the portal of entry. Thus, one cannot be sure the increase in staphylococcal infections is a real one; we have never had patients like some of these before. The third factor is the influence of the antibiotics. The antibiotics have failed to answer the staphylococcal problem, and thus it stands out like a sore thumb. I think there is no question the antibiotics have encouraged development of antibiotic-resistant organisms or allowed the existing ones to become the predominant strains, and this has happened with so many antibiotics that one cannot reasonably ask, "How do you know these strains weren't going to do this when you discovered the antibiotic?" There is too much coincidence; every antibiotic goes through the same pattern.

Also, antibiotics actually may, by prolonging life in certain patients, invite other things. For instance, patients who have pulmonary infections, the patients with postoperative pneumonia who might otherwise die in the first few days of the illness, live to have staphylococcal pneumonia superimposed on the original aspiration and atelectasis. This type of process is so much in the foreground that when one looks at the total staphylococcal problem I think one can say quite definitely that statistically staphylococci are causing more deaths

than they did formerly but they are not necessarily causing more deaths of the same type of patients we were observing in about 1939. A recent article by M. Finland, W. F. Jones, Jr. and M. W. Barnes entitled "Occurrence of serious bacterial infections since introduction of antibacterial agents" brings out this statistical evidence very clearly (J.A.M.A. 170: 2188-2197, 1959).

Natural Bacterial Inhibition of Organisms

DR. POTH: Dr. Lepper, would you discuss the question of the natural bacterial inhibition of organisms?

DR. LEPPER: Microbial competition in various areas has been very difficult to define and study. On the basis of the relatively few areas studied in the experimental animal, I think it is quite clear that bacteria can and do compete for areas of predilection. The best evidence, I believe, is that some extra implantation does occur in man following the use of broad-spectrum antibiotics. Studies published by our group showed that with a broad spectrum of activity there were more implantations of staphylococci than expected from an estimation of a control group not receiving antibiotics. On the other hand, with a drug with a limited spectrum, like penicillin, a fairly accurate prediction of implantations in the respiratory tree could be made, using the rate of implantation in the untreated patient and allowing for the usual antibacterial effect of penicillin. Moreover, distribution of sensitivity patterns were also predictable.

It is likely that the broader spectrum limits the normal flora, and, since the shift toward the more resistant form is even greater than one would expect from the effects of the drug on the *Staphylococcus* per se, the best inference is that this is probably a related effect on the other microbes, which probably, in the normal course of events, keeps the *Staphylococcus*, at least in adults, pretty much out of the mouth and pharynx except for very small numbers, and limits them to the anterior nares.

DR. POTH: Would you define the word "phage" and also tell us whether the so-called phage 80-81 strain of staphylococci might not be coming to the fore because of conditions in which various types of organisms capable of supporting phage growth lytic to the *Staphylococcus* do not exist because of the widespread use of antibiotics?

DR. LEPPER: A phage or bacteriophage is a virus that infects bacteria, and these phages infect bacteria fairly specifically. A certain phage will attack a certain bacterium. Consequently one can use them as labels. If phages 80 and 81 attack a certain *Staphylococcus*, then this is a label, and if phages 52 and 52A attack another strain, you know this is another strain. For epidemiologic use, it is a fairly satisfactory label. If one uses such a label, just as one uses a serologic label in other circumstances, one will see that the phage types vary with time within the community. Some phage types that were predominant back in 1951 and 1952 are rare now. However, 80-81 is a rather complex group, and apparently there are several subtypes.

As to the problem of virulence, it seems that right now virulence is related to certain of the strains that are lysed by phage 80-81 alone or among other combinations. Other strains lysed by 80 or 81 or both, with or without other phages, do not seem virulent. So we do not know too much about the subtle relationships of phage types to virulence, and all we can do is speculate. It certainly is an interesting fact that with diphtheria bacillus, phage transfers the virulent factor. One can infect an avirulent diphtheria bacillus with its appropriate bacteriophage and the diphtheria bacillus then becomes a toxin producer. There is some speculation that certain phages, when they do spread to organisms, may take a virulent factor along with them.

DR. POTH: We have observed in our hospital that most of the serious infections in hospital personnel occur in medical students and young nurses in the beginning of their service and that after a year or so they are much less susceptible to infections. Is it possible that a certain degree of immunity or resistance to these organisms develops?

DR. LEPPER: It is quite likely that the younger individuals are more susceptible to *Staphylococcus*, just as they are to most infec-

ious organisms. I am quite sure that the really common form of staphylococcal disease is chronic and subacute furunculosis, usually a disease that lasts about three to six months; that this is a self-limited infection in most persons; and that it probably is terminated by the development of immunity and immune mechanisms that are very similar to any other bacterial infection.

However, the predominant phage type we have been seeing recently does not always involve the youngsters. My consultation practice is made up almost exclusively of surgeons who have furunculosis and are worried about operating. They take a vacation to Florida and then they take one to Hawaii or someplace, and then they cannot afford another vacation and come around wanting to know what to do. Because this is a three to six month problem, it can be quite a great one for the surgeon. I have seen about 15 or 20 men in the past three or four years with this syndrome.

Carriers

DR. POTH: I am going to direct this next group of questions to Dr. Smith and let him select the ones he would like to talk about, and then ask Dr. Lepper to discuss the points further.

In which hospital personnel should cultures be made to detect potential *Staphylococcus* carriers, and how often? What are the criteria for stigmatizing the hospital employee or staff member as a carrier? What must the hospital staff do with known carriers? What restrictions must be placed on their contact with patients in the operating room? What about contact with infants, elderly debilitated patients, patients who have serious metabolic diseases, and patients receiving steroids?

DR. SMITH: Before we talk about the nebulous state of being a mysteriously innocent carrier—a typhoid Mary who hasn't yet been told—I want to ask a question. Who has the boils, the furuncles, the paronychiae, the infections of the skin and body, the draining acne, the obvious clinical infection, and is still caring for these potentially infected people?

DR. POTH: Would you differentiate between the nasal carrier and the spreader and the person who has organisms other than in the nasopharynx?

DR. SMITH: That is a good word, "spreader." Ninety per cent of the personnel in our hospital who have had staphylococcal infections due to coagulase-positive, antibiotic-resistant organisms in the past year have been nurses and nurses' assistants, the people who handle the dressings and the patients' bodies. They have had the infections. We call them spreaders. Contrast that with the carrier, the person who innocently, without evidence of clinical infection, has the same strains apparently residing in his nose, as shown by careful bacteriologic culture of the anterior nares.

Is a one-time culture enough? We made cultures in 667 persons employed in all parts of our hospital last summer. Thirty-eight per cent showed the so-called hospital strains, the virulent strains. Not a single one was a spreader. We could not find a clinical infection among them, but they carried "staph" in the nose. Can we call these persons chronic carriers on the basis of one culture? Absolutely not. It is known that some of these people, particularly if they retreat from the patient, will lose the strain; oddly enough, when they come back to the patient they may acquire it again. They may be living in some sort of a symbiotic state with the organism, but they are not infected.

DR. POTH: Would you put such a person in the nursery or in contact with elderly debilitated patients over long periods, hours a day? In contrast with the short contact a physician might have with such a patient, the nurse might spend eight hours with him.

DR. SMITH: Our physicians put in longer hours than any nurse and certainly have a lot more contact with the patients!

DR. POTH: The physician is not in contact with the same patient for eight hours. I think it is very seldom that any of us ever spends eight hours a day with one patient.

DR. SMITH: Seldom indeed.

DR. POTH: If we did, we'd talk about it for a long time to come.

DR. SMITH: On my service it is the junior resident who sits by the bed all night, and he gets the infection. My definition of a carrier

is any member of the professional or subprofessional staff on my service who on two or more occasions has one of the two major virulent strains in the hospital cultured from his nares. These strains are 80-81 (which now account for 50 per cent) and 53-VA-4. There are other strains, but these two are the ones we worry about. If on two occasions these strains are cultured, the employee is removed from all contact with patients and is sent to the research laboratory or the pathology laboratory. This, however, does not fit in well with the concept of nursing, and it is a difficult problem to figure out what to do with a nurse who happens to be carrying a virulent strain.

We have not treated any of these people actively or aggressively. We don't know whether or not we can. We do not know whether medicolegally we can impose the risk of antibiotic therapy on a person who just happens to be standing by when the bug comes along, and I wish somebody would tell us how to eradicate the carrier without sending him out of medicine for the rest of his life.

Certainly no one who is a carrier of strain 80-81 or 53-VA-4 in our hospital should deal with the open wound, the susceptible patient, the one receiving cortisone and steroids, the patient who is a "sitting duck" for staphylococcal infection.

DR. POTH: Would you keep a surgeon from operating if he is an incidental carrier?

DR. SMITH: We can keep the consultant out of our hospital but we cannot keep him out of his private practice. We had two residents who succumbed to life-threatening infections while caring for surgical patients 16, 18 hours a day. They came down with extensive cellulitis due to 80-81 *Staphylococcus*, but before they were absolutely disabled they spread it all over the place; sturdy fellows that they were, going to die in their tracks. So we do have both spreaders and carriers.

When an employee has an active infection on the body due to one of these staphylococci, you will nearly always find it in the nose. The reverse is not true. There are many innocent carriers without signs of clinical infection. The spreader is vicious. Nobody should be allowed to care for anyone who is sick from even a common cold these days if he has an active clinical infection in or on the body.

DR. POTH: Dr. Lepper, what do you consider a dangerous carrier?

DR. LEPPER: I think I agree with what has been said. I am sure I agree that the person with furunculosis—active staphylococcal lesions—has been the one who has been incriminated the most, and for good reason. This person has a highly infected skin, not only at the site of the lesion but also over the various folds of the body. I think one of the mistakes frequently made, in the person with recurrent furuncles, is the use of a so-called airtight pad over the lesion. The staphylococci do not necessarily spread from the boil; they spread from all over the skin.

As to the problem of the nasal carrier, there is no question that about one-third to one-half of the adults do carry coagulase-positive organisms in their noses, and there usually is a predominant phage type. We have seen phage types come and go now over the past eight or nine years, and there is no question in my mind that they do go through hospitals in waves. This is the reason some hospitals will not have a problem of resistant staphylococcal infections for quite a while and then all of a sudden will find they do have a problem.

The one-third to one-half of the personnel who carry phage types fall into two categories. There are those who hold onto a phage type for dear life. Some of our personnel have carried the same phage type for as long as three years. They constitute about 20 per cent of the carriers, and usually they do not spread much disease because the organism they carry is one of a previous era and is not causing much disease at present. They do not participate much in this "ping-pong" business between the patient and the personnel that tends to transfer rapidly the resistant organisms to each new patient brought in.

The other category is a group of carriers we call the rapid exchangers, and these will exchange phage types very rapidly—several in a period of a few weeks. Sooner or later these persons usually latch onto one type that is virulent.

Obviously one cannot take 50 per cent of

FIGURE 2.

the personnel out of service. I think all one can do reasonably is remove the person who has furunculosis. Can any of the nasal carriers be incriminated epidemiologically? Epidemiologists can put the finger on a nasal carrier who does not have skin lesions but who may be a fairly dangerous spreader, if they make a reasonable surveillance of the hospital situation. We should have a minimal requirement for epidemiologic evidence to incriminate a nasal carrier and take him out of service; otherwise we cannot run the hospitals.

DR. SMITH: This epidemiologic evidence is a fine-sounding term for having presumptive evidence to point the finger at a person, an employee, who is carrying the virulent strain. Right?

DR. LEPPER: Yes.

DR. SMITH: We have no right, if there are 20 people working on a ward and eight of them are carriers of the same strain, to say that any one person was guilty unless an infection or infections occur that identically match the phage type found in the one employee. We are all saturated with it. Fifty per cent of my anesthesiology group, eight residents and five or six consultants and two staff men, are carriers the year round.

DR. POTH: Are they kept out of the operating room?

DR. SMITH: They are not carrying the virulent strain—yet. However, when they get eliminated we will close down.

One of our nurses on a busy general surgical ward of 52 beds was responsible for seven infections. We were able to show that the phage type matched. Without question, on this presumptive epidemiologic evidence, this one nurse was responsible, because no other employee on the surgical service during that month, the preceding month or the following month carried the same phage type. This unfortunate girl had to be asked to leave.

DR. POTH: Whose hospital did she go to?

DR. SMITH: I don't know where "staphylococcal Susie" is, but mind you, once we find a carrier of a virulent strain we get anal smears. We made a study that showed that we would have missed 30 per cent of our carriers if we had not also cultured the stool or the anal material. In other words, a large number of persons whose nasal cultures are negative will have positive stool cultures. I do not know the significance of this. I only hope they are washing their hands well after they go to the bathroom.

DR. POTH: If your staff is like mine, the residents watch you wash your hands and wonder why you do it, because they don't wash theirs.

The important distinction to make here is between the person who is carrying the organism in his nose but is not spreading it and the person who is truly a spreader. In view of the large numbers of carriers in the hospital population, the very practical problem arises of how to run the hospital if all of them are to be taken out of contact with patients. Also, how soon after a patient comes into the hospital does he himself become a carrier if he is in a heavily contaminated area? The answer is about two weeks. Now, your new clean employees come in, and within two weeks 50 per

cent harbor the organisms. What are you going to do? Are you going to pension them? This is a very difficult problem, and certainly has not been solved.

Comment

Unfortunately we have been unable to touch on all the problems presented by this subject of resistant staphylococcal infections, but I hope we have given some insight into its overall aspects. It is not something which is particularly new. We have had staphylococcal infections with us for a long time, and we are going to have them with us for a long time to come. If we could graft a surgical conscience onto every person connected with medicine, from the administrator on down to the charwoman, I believe we could stop being too anxious about staphylococcal disease. We would have it under fairly good control, because that is exactly the way we do control it in every area. We clean up the place, and practice the type of medicine and surgery necessary when we do not have an agent which is specific against a particular organism. There are some strains of organisms for which no antibiotic has been developed. Proper use of antibiotics is of tremendous help in controlling this overall problem. Resistant organisms are going to give us trouble. Their characteristics are going to change. We are going to have still other types. We must expect this problem to change continually. Continuous vigilance, morning, noon and night, day in and day out, is mandatory, just as it was 20 or 25 years ago.

DR. SMITH: The real need, then, is for a return to aseptic thinking and aseptic habits. The surgical conscience is only an expression, we hope, of the most skillful aseptic practice—in other words, a return to principles that have never been disproved. There is no such thing as a bacterium that becomes resistant to asepsis. The trouble, then, eventually, can be traced to us, to people, not to anonymous things or floors or walls. Figure 2 depicts the trouble in our hospital and in all the hospitals across the country—the surgeon who just does not accept the situation as it exists.

Postgraduate Clinical NOTES

137. THE CHANGING PATTERN OF LIFE-THREATENING MICROBIAL DISEASE

It is clear that there have been dramatic shifts in the nature of life-threatening microbial infections in the past 20 years. It seems probable that the use of potent antibacterial agents has in part forced this change. It is equally clear, however, that medical science has not been able to protect human patients from infections that can produce death. The present observations reinforce the thesis recently elaborated by Dubos. In essence, microbial disease appears to be an integral part of human life and death. Although one can manipulate the situation and thus select the microbial agents that will establish progressive disease, a significant number of hospitalized patients on medical services continue to die of infection in the present day. These deaths are caused primarily by gram-negative bacilli and fungi that inhabit the gastrointestinal tract, by staphylococci insusceptible to present antimicrobial agents and by viral agents for which no drugs are available. In the majority of cases these infections are superimposed on other serious diseases that initially prompt hospitalization.

David E. Rogers, The changing pattern of life-threatening microbial disease, *New England Journal of Medicine*, October 1, 1959, pp. 682-683

Self-help Devices:
Transfer Onto and Off a Bed

EDWARD W. LOWMAN AND HOWARD A. RUSK

Institute of Physical Medicine and Rehabilitation
and the Arthritis Self-help Device Office*

New York University-Bellevue Medical Center, New York

THE height of a bed is often an important factor in enabling a patient to transfer onto and off it by himself. The ambulatory patient with involvement of the hip or knee or both will have less difficulty if the bed is high, thereby reducing the stress on the hips and knees. In the case of spinal rigidity, the bed may be used as a fulcrum; and the higher the bed, the easier it is for the patient to transfer in and out of it. Patients in wheel chairs, on the other hand, will find it more satisfactory to adjust the height of the bed to the height of the chair.

FIGURE 1. The simplest method of raising the height of a bed is to use wooden blocks. These can be home-improvised, made to specification by a local carpenter, or purchased from local hospital supply houses. Some patients have successfully solved the problem by filling well-made metal cans with sand and resealing them.

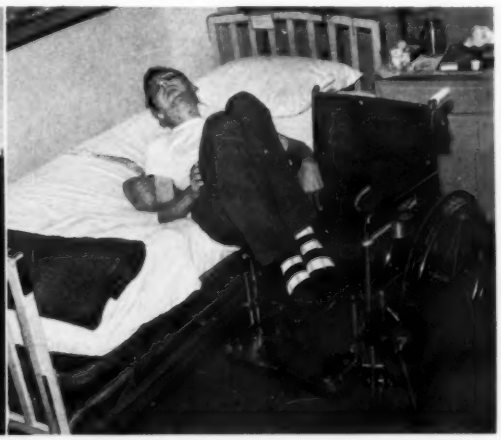


FIGURE 2. Transfer of the patient from bed to wheel chair is best accomplished in the horizontal plane; a wheel chair having removable arms expedites the procedure.

*Supported at the Institute by the Arthritis and Rheumatism Foundation.

FIGURE 3. At times a bridgeboard or slide board may be needed to cover the gap between the chair and the bed. These boards can be made at home or purchased from a local hospital supply house.

FIGURE 4. A home-devised rope ladder will assist in rising from a supine to a sitting position at the side of the bed. A commercially available unit called Posey-Aid can be purchased from most local hospital supply houses for about $6.00.

FIGURE 5. *Left.* A bedrail may be used for support and aid in assuming the erect position. An upright pole or sturdy chair secured close to the bed may offer the same type of help.

FIGURE 6. *Right.* At times a single overhead trapeze may be indicated. This unit was made at the Institute of Physical Medicine and Rehabilitation, but several similar types are available from local hospital supply houses.

FIGURE 7. In the more severe types of disability, such as ankylosis of the spine and hips with marked limitation of knee and ankle motion, a more complicated overhead trapeze system facilitates transfer from bed to wheel chair. The patient must have good use of the upper extremities to manage in this manner.

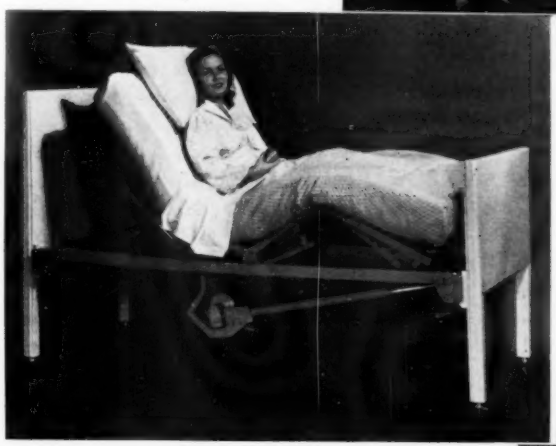


FIGURE 8. Although the motorized bed positioner is somewhat expensive, it permits the patient to raise and lower the head and foot of the bed by minimal pressure on a switch within reach. Unaided, the patient can assume a sitting position as the first step in transfer off the bed. This unit is manufactured by Self-Ease Units, Inc., 1026 Park Avenue, New York 28, but it can only be installed in a Gatch bed.

FIGURE 9. Many patients who are partially or completely ankylosed in an erect position cannot bring themselves to a standing position, but are able to ambulate once this position has been assumed. A unit such as the Ortho-Therapy Bed may mean the difference between the patient's being totally or partially bedbound.

A brochure describing the units may be obtained by writing to Franklin Hospital Equipment Company, 116 Academy Street, Newark, New Jersey.

For the patient who is completely unable to manage by himself, a Lifter may be indicated to reduce stress on the family (figure 7, page 881, December issue). Motorized units require minimal effort by the patient, and even the most severely handicapped can be self-sufficient to some degree. Selection of a Lifter depends on many factors and thorough investigation should be made before purchase. A listing of manufacturers of the units is available from the Arthritis Self-help Device Office, Institute of Physical Medicine and Rehabilitation, 400 East 34th Street, New York 16.

Readers are invited to submit suggestions and ideas for devices they have developed and would like to share with others. Forward all such suggestions and comments to: Editorial Department, POSTGRADUATE MEDICINE, Essex Building, Minneapolis 3, Minnesota.

SYMPOSIUM

Renal Failure

ROBERT M. KARK,[1] WILLEM J. KOLFF,[2]
VICTOR E. POLLAK[3] AND EDWARD J. BEATTIE, JR.[4]

Modern methods of treatment of acute and chronic renal failure are much improved over those of 10 years ago, but before vigorous treatment is instituted one must be sure it is given by the right hands in the right manner.

Dialysis with the artificial kidney may be lifesaving and should be employed earlier when indicated. Use of the artificial kidney is not simply a matter of having the unit available; it also requires highly trained personnel.

Many lives could also be saved by preventing renal failure. Important points in recognizing impending failure are stressed.

In chronic renal failure, synthetic diets provide for accurate regulation of nutrients. The "antipotassium cocktail" is helpful in preventing potassium intoxication, as are the potassium-binding resins.

DR. ROBERT M. KARK (Moderator): We are going to talk informally about renal failure. As you know, there are two kinds of renal failure, acute and chronic. I suppose that one recognizes acute renal failure by the fact that the patient either is anuric (and this is not very common) or is oliguric. Oliguria is defined differently by different people. Usually if a patient is taking a lot of fluid and passes less than 350 cc. of urine a day, one can say he is oliguric; an older patient may be oliguric when he is passing 400 cc. of urine a day. In chronic renal failure, the patient may be passing large amounts of urine because he has a fixed specific gravity and uremia develops.

The surgeons seem to see many more cases of acute renal failure than do the physicians. I don't know why this is, but Dr. Beattie will perhaps tell us the kind of patients he sees who have anuria or oliguria.

DR. EDWARD J. BEATTIE, JR.: One of the first things one should be sure about when a patient allegedly has renal failure is that he does

[1]Professor of Medicine, University of Illinois College of Medicine, Chicago, Illinois.

[2]Associate Professor of Experimental Medicine and Head of the Department of Artificial Organs, Cleveland Clinic, Cleveland, Ohio.

[3]Research Assistant Professor of Medicine, University of Illinois College of Medicine, Chicago, Illinois; Established Investigator, American Heart Association.

[4]Professor of Surgery, University of Illinois College of Medicine, Chicago, Illinois.

Presented before the forty-fourth annual Assembly of the Interstate Postgraduate Medical Association at Chicago.

ROBERT M. KARK

WILLEM J. KOLFF

VICTOR E. POLLAK

EDWARD J. BEATTIE, JR.

not have urinary retention. More than one case of "renal failure" has been cured with a catheter. The patient may have more than urinary retention, which usually can be handled by one catheterization or continuous catheterization. He may also have an actual block in the urinary tract.

The next two situations probably are the ones we encounter most commonly. The first is dehydration. The "water-balance pendulum" has swung to the opposite extreme. It used to be that the surgeons were guilty of giving excess fluids to patients. On our surgical service we dehydrate more people than we overhydrate. Then there is the question of salt balance. The surgeons in years gone by gave too much sodium chloride to their patients postoperatively. Again the pendulum has swung the other way, and more times than not we give too little sodium chloride postoperatively. Hyponatremia is frequently a cause of oliguria, if not total anuria, postoperatively.

Finally, we still see some instances of so-called lower nephron nephrosis in which patients have accidentally received incompatible blood or shock has occurred. The heart-lung bypass procedures produce a fair amount of free hemoglobin in the blood serum in a situation where renal flow and urinary output may also be impaired.

DR. KARK: I am glad to know you do not overhydrate your patients. This is a common mistake that physicians used to make, and some of them still do. We used to call it Harrington's syndrome. Sir John Harrington, the favorite courtier of the first Queen Elizabeth, was the man who invented the water closet. Harrington's syndrome is a situation which is iatrogenic, that is, induced by doctors who, when they have a patient who is not passing urine, employ the same means as do housewives who are trying to fix a blocked water closet; they try to flush out the works. They pull the plug and nothing happens; they pull it a second time and nothing happens; they pull it a third time and the whole thing overflows. This, of course, happens to patients when you infuse large amounts of saline when they are anuric; the fluid overflows into their tissues and they become edematous. Of course we do not do that these days. We treat them in another manner. Dr. Kolff, what do we do?

DR. WILLEM J. KOLFF: It is very difficult in this world to be original, and I do not claim any originality in the development of the artificial kidney. The disposable artificial kidney now available commercially is a further development on several artificial kidneys that were available previously. In the center are two tubes distended with blood. Through the cellophane surrounding the blood, dialysis takes place. The smaller molecules go out and the larger molecules and red cells are held back, and at the same time a rinsing fluid goes through the screen surrounding this tubing and equilibrium takes place between the electrolytes in the bath and the electrolytes of the patient's blood plasma. If you get the proper constitution of the electrolytes in the bath, at the end of the dialysis the patient's electrolytes will be the way you want them to be.

The next problem was to wind this material around a core. Presently, all commercially available artificial kidneys are made around

fruit-juice cans or their equivalent. When you put the fruit-juice can into another larger container, you have a disposable dialyzing unit that you use only once. The large container holds 100 l. of rinsing fluid. We do not throw away the larger container, but the dialyzing unit in it is discarded after use.

In a uremic patient who is desperately ill, we use the saphenous vein to obtain the blood for dialysis. This has the advantage that the treatment is quite independent of the blood pressure. Actually, in several instances we have performed dialysis while the patients were undergoing cardiac massage; in such a situation you can reduce the potassium and see that the heart picks up again.

I would be open to severe criticism if I created the impression that the artificial kidney is the only answer for the treatment of uremia. As has already been mentioned, we do not want to overload a patient who cannot excrete any water, so we give them 500 cc. per day. Would you give more, Dr. Kark?

DR. KARK: I don't think so.

DR. KOLFF: I don't give them any salt, because they don't excrete any salt. I am pretty sure Dr. Kark doesn't give them salt either. As to suppression of protein breakdown, we try to give these patients a high-calorie, low-protein diet. You must take into account that some patients will have to live for 40 days or so almost without renal function. If you do not feed them properly you will certainly end up with a wreck by that time.

We like to give them erythromycin to avoid infection—erythromycin rather than other antibiotics.

Finally, to eliminate the products of retention, I personally prefer the artificial kidney, although I know that peritoneal lavage can be used and I have used it many times. One of the main drawbacks is that you are never quite sure whether the patient has peritonitis or just a chemical irritation, as it is called, of the peritoneal cavity. Intestinal lavage is extremely difficult, and I am sure you wouldn't want to try that.

Presently there are 185 artificial kidney units in the United States. Use of the artificial kidney is not simply a matter of having the unit and connecting your patient to it. True, dialysis can decrease any degree of uremia to a respectable level and it can bring your patient into good clinical shape, but you must be trained to do it. We use a four-channel recorder to record the electrocardiogram, and we have a scope so we can follow it. This is difficult work, and we recommend that a hospital that wants to use an artificial kidney send us a man whom we can train for this particular job.

DR. KARK: Why do you need a scope and a recorder?

DR. KOLFF: I will admit promptly that some of these patients will die while being treated with the artificial kidney. Some will die in the ambulance on the way to the hospital. Some have died in the hall, and one patient died in the elevator. In comparison, only a few have died during dialysis. We want to see the electrocardiogram because we are bringing about tremendous changes in the electrolytes, many of which we do not understand. Here we come back to the tailor who, when told that a suit he had made didn't fit quite properly, replied, "The art of tailoring has not degraded as yet to an exact science." The same is true for the treatment with the artificial kidney, and when you can see in the scope that something is going to happen or is happening to the heart rate, you had better stop, because your patient is still alive. Does that satisfy you?

DR. KARK: Yes.

DR. KOLFF: The next question that arises (and I am surprised that Dr. Kark hasn't asked it) is: Do these patients really need the dialysis? I will try to answer that by reviewing a few of our results. During 1957 we treated 38 patients with the artificial kidney. Nineteen recovered, and 18 died. One patient improved; he did not recover because he had a cancer. The 18 patients who died included three with irrecoverable renal disease, five with irrecoverable complications, and six with irrecoverable underlying disease. When your patient is dead, the chips are on the table and you have your postmortem; you can nearly always determine whether he was potentially recoverable or was doomed anyway. If his renal arteries were both blocked by clots, he was ir-

recoverable. If he had a carcinoma all over his peritoneum, he was irrecoverable. You did not know that when in the middle of the night you received the patient for treatment with the artificial kidney.

I have accounted for 14 of the 18 patients who died; four are missing. Those, of course, can be held against us and are so many black spots on my soul. Those four I recall. One was a man who had a knife through his chest, through his diaphragm, through his stomach. He was sewed up at another hospital. His wound disrupted. He was sewed up again. He was brought to us very ill, and was treated with the artificial kidney. Renal function recovered, and we failed to recognize that one of the large sutures which had been used to close his wound had caught his jejunum, and that is why he died. Another patient died from potassium intoxication on the sixteenth day, which we failed to anticipate. Another had an empyema of the chest and after 13 days pulled out an indwelling catheter. The fourth patient died for reasons unknown within 24 hours of admission. He is classified as recoverable to give him the benefit of doubt. This was in 1957. In 1958 we did considerably better, and I am quite sure that in that year we did not lose a single patient who was potentially recoverable. In 1959 we lost one patient, an elderly man, from a myocardial infarction 14 days after a transfusion accident.

Perhaps I can demonstrate what can be done with an artificial kidney by describing a patient who was found comatose on the bathroom floor. Nobody knew exactly what was wrong, but when she awoke she had hemiplegia and total anuria. This patient with hemiplegia received physical therapy and was treated with the artificial kidney seven times. After 30 days of almost complete anuria, she was still a little paralyzed on one side of her face. When you get a patient and you don't know what is wrong, all you can do is treat him as well as you can until his condition is good enough for you to proceed with further diagnostic studies. It was found, after 30 days, that this woman had a complete necrosis of the cortices of both kidneys.

When you have a patient who has a high blood urea level and a low alkali reserve, can you, on the basis thereof, predict that he is going to die or is going to recover? Absolutely not. If you treat him properly with dialysis, it makes no difference whether the blood urea is higher than 300 or lower than 300 when you get him, as long as he lives long enough to be dialyzed. Of 11 patients whose blood urea levels were higher than 300 mg., six recovered. Of 27 patients with blood urea levels between 100 and 300, 14 recovered. Both groups demonstrate a recovery rate of about 50 per cent.

We have also found that if the carbon dioxide level of the blood is extremely low, that is, less than 10 mEq. per liter, the patient has Kussmaul respiration. These two always go together. Thus, if a patient has Kussmaul respiration and has uremia, you can be certain that his carbon dioxide will be low.

I would like to present a tape recording of Kussmaul respiration made during a conversation with a patient with severe uremia, just before treatment with the artificial kidney.

DOCTOR: Do you know where you are now, Mr. J.?

PATIENT: Yes.

DOCTOR: Where?

(It takes him a long time to answer, which is quite typical.)

PATIENT: Cleveland Clinic.

DOCTOR: Now, start at 50 and count up to 100 by 3s.

PATIENT: 50, 53, 56, 59, 62, 73, 75. . . .

(This man was an accountant. The deep gasping Kussmaul respiration can be heard.)

PATIENT: 88, 91, 94 . . . my God!

Now I would like to present a recording of the same patient two days after treatment with the artificial kidney.

DOCTOR: How are you feeling?

PATIENT: Feel fine.

DOCTOR: What do you feel like?

PATIENT: I'm hungry, I'm starved. I want to eat. It's 12 o'clock and I'm hungry.

DOCTOR: How does it feel to be sitting up?

PATIENT: It feels very good. Yesterday I was in bad shape, I know that. I woke up screaming. I was so weak I was wondering what was the matter with me. I didn't even

know what happened. Today I feel strength in my limbs anyway.

DOCTOR: Will you breathe for me, just normally. (His respiration is perfectly normal.)

DR. KARK: Thank you, Dr. Kolff. That was a very interesting demonstration of the value of the artificial kidney.

Differential Diagnosis of Cause of Oliguria

As doctors, we are all interested in knowing something about the differential diagnosis of patients with anuria, and one of the things we often encounter is a patient who instead of being anuric from renal failure is anuric because he is dehydrated. This happens commonly to patients with chronic renal failure, and I wonder if Dr. Pollak would tell us something about the differential diagnosis of patients with acute renal failure versus patients with acute dehydration.

DR. VICTOR E. POLLAK: This is often a difficult clinical situation. It is relatively easy to make this differential diagnosis when one knows the antecedent history. For example, it is extremely unusual, I would say, for a patient with known chronic renal disease to get a superimposed acute tubular necrosis. If one knows the patient has chronic renal disease beforehand, then the problem usually can be solved on the basis of the history. An additional important factor here is the history of fluid and salt intake immediately preceding the oliguria.

One of the situations when the patient with chronic renal disease frequently gets into trouble is when he is well compensated, perhaps able to work, and so on, and then something acute happens—perhaps an accident or the necessity for an operation for some reason or other. If it is not recognized that the patient has renal failure and that he usually requires more salt and more water than does a patient without renal failure undergoing this form of stress, he may lose salt and water very rapidly through the kidney and present oliguria. When this happens after a surgical procedure, it may be very difficult indeed to make a differential diagnosis between acute tubular necrosis and chronic renal failure with oliguria, particularly if nothing is known of the renal status prior to operation. The best way to make the distinction, having taken a history and examined the patient, is to assess clinically whether or not there is substantial dehydration. If there is, this may be due to either chronic or acute renal failure, and is much more likely to be due to chronic renal failure. Under these circumstances one can give the patient a test infusion. We have heard from Dr. Kark and Dr. Kolff already that we do not want to overload these patients with fluid, but under certain circumstances it may be permissible to give an infusion of 1000 to 1500 cc. and measure the output of urine fractionally hour by hour over the next few hours. In this way one can readily determine in most instances whether or not the patient is capable of putting out urine. Unfortunately the matter is not always so easily resolved, and 1500 cc. in a severely dehydrated patient may not give you an immediate answer. Only if the patient is severely dehydrated is it permissible to go on with a little more fluid, and it must be given cautiously.

DR. KARK: Dr. Beattie told me about an interesting case which presented this sort of problem, and perhaps he could summarize it.

DR. BEATTIE: I mentioned to Dr. Kark before this discussion that there can be no disagreement that when a patient who has serious renal failure is about to die, the artificial kidney and dialysis may be lifesaving. On the other hand there is no question that many lives could be saved by preventing renal failure, at least acute renal failure, if we were more careful and alert to it. I obtained the summary of one of our less successful cases, and it might be worth going over to illustrate some factors of importance.

The patient was a 68 year old man who had had resection of the jaw for carcinoma and had done well until, unfortunately, two new carcinomas developed, one in his larynx and one in his lung. At the time of admission to the hospital, his nonprotein nitrogen level was 35, and urinalysis disclosed a concentration to 1.007 and yielded negative findings for protein, leukocytes, red cells and casts. We felt that a thoracotomy was indicated for purposes of biopsy, since bronchoscopic study gave

negative results. On the day of operation he received 1500 cc. of intravenous infusion; none of this was salt. He received a transfusion of 500 cc. of blood, and that day he passed 200 cc. of urine. The first day after the operation he did not take fluids as well as he should have. He was a little bit depressed. He was hoarse and could not cough well. We had to give him 2000 cc. of intravenous fluid the first day postoperatively, of which half was isotonic saline. He took 450 cc. by mouth. With this 2,450 cc. intake, he put out 450 cc. of urine. We thought he was a little bit dehydrated. The second day postoperatively we again gave him 1700 cc. intravenously, of which 6 gm. was sodium chloride, and 400 cc. of liquids by mouth. Of this 2100 cc. intake, he put out 200 cc. of urine but was incontinent several times, so we were not sure of the exact amount excreted. The third day postoperatively, he received 2,250 cc. intravenously, plus packed red cells, since he was a little anemic. He put out 750 cc. of urine, which concentrated to 1.009 and contained an occasional white cell and red cell, a few hyaline and granular casts, and no protein.

At this point we began to realize we were in trouble, since this man was putting out a urine with a specific gravity of 1.009. The fourth day we gave him 2300 cc. intravenously, of which 8.5 gm. was sodium chloride. Blood chemistries at that time showed a nonprotein nitrogen of 155 mg. per cent, a sodium level of 135, a potassium level of 5.6, a chloride level of 100, a carbon dioxide content of 20 mEq. per liter, but he put out 1200 cc. of urine that day. On the fifth day he received a total of 4000 cc. of water. He put out 1500 cc. of urine, and the blood sodium level was 135, potassium 5.6, chloride 109, and carbon dioxide 22.3; but the nonprotein nitrogen level had risen to 170, and that evening he died.

Here was a man who had compensated renal failure with a specific gravity of 1.007 on admission, and we as clinicians did not recognize when we were headed for trouble; we got behind, and lost the patient unnecessarily.

DR. KARK: This is a very interesting case. The only comment I wish to make about it is that when patients are to be operated on, one always orders "Examine the urine!" If you find any abnormality, such as a low specific gravity near 1.010, you certainly ought to investigate renal function thoroughly before the operation. If the laboratory sends back a report "q.n.s. for specific gravity," they are old-fashioned. Nowadays we have refractometers that can read solids with just one drop of urine or one drop of plasma, and with that the laboratory certainly never ought to report "q.n.s."

DR. KOLFF: An explanation of what has been done wrong is always useful, but I cannot help wondering why this man was not treated with dialysis about the day before he died. I think I heard a nonprotein nitrogen level of 155. Wouldn't dialysis be indicated?

DR. BEATTIE: We did not have the artificial kidney available then; we do now.

DR. KOLFF: It is not impossible to put a patient like this one in an airplane and fly him to a place where there is an artificial kidney available.

DR. KARK: That is certainly true; however, this patient, although he did have a nonprotein nitrogen of 155 at that time, demonstrates that high nonprotein nitrogen levels can develop when dehydration and chronic renal disease are present, and these patients also can be treated very well sometimes without artificial kidneys.

DR. BEATTIE: I would like to amplify my last statement. This patient's blood chemistries were still normal except for the nonprotein nitrogen. I do not want to go into all the other problems. He had three cancers and a tracheostomy, and there were contributing factors to his demise, and even if the artificial kidney had been available I am not sure I would have used it right at that time—although I certainly do agree there are obvious indications for dialysis.

Diseases Which Produce Acute Renal Damage

DR. KARK: Dr. Pollak, would you tell us something about the various types of disease which produce acute damage to the kidney with oliguria.

DR. POLLAK: From a practical point of view it is reasonable to divide these conditions into

reversible and irreversible types. As Dr. Kolff pointed out, frequently it is quite difficult to determine, when the patient is acutely ill, whether he has reversible or irreversible renal disease.

There are some things one can take into account in arriving at a diagnosis, however. One is the cause of the renal failure. Is it due to a poison such as mercury or carbon tetrachloride? Is there an antecedent history of obstetric difficulty such as might lead to acute cortical necrosis, severe preeclampsia, concealed accidental hemorrhage? Is there a history of operation and, if so, exactly what happened during the operation? The anesthetic chart should be inspected with great care, particularly for the level of the blood pressure during the operation. The combination of a period of hypertension with hemolysis is quite common nowadays in situations in which surgeons are doing massive operations with extracorporeal circulation and there is a considerable amount of circulating free hemoglobin.

Most important of all, is there any obstruction to the outflow of urine? This may result in complete anuria. Certainly a cystoscopic examination should be done and, if necessary, catheters put up the ureters to insure that there is no obstruction to the outflow of urine.

Of these causes, many are recoverable in time. Acute cortical necrosis following concealed accidental hemorrhage is one which sometimes is not. What of the irrecoverable ones? These fall into the category of diffuse renal diseases such as acute glomerular nephritis with rapid progression to involve all the glomeruli in a manner which is much more severe and more rapidly progressive than the usual type of disease that we see. This occurs sometimes in lupus erythematosus, in polyarteritis nodosa, in other rarer diseases such as thrombotic thrombocytopenic purpura. There are other situations in which the renal artery or the renal vein may be suddenly occluded bilaterally. All such patients, who may be very ill, should be treated by all available methods, including dialysis, but there comes a time when one needs to know whether or not they have reversible renal disease. For this purpose a renal biopsy can be done, giving one an accurate idea of the reversibility or irreversibility of the disease. Renal biopsies have been done safely in acute renal failure in large numbers, particularly by Dr. Brun of Copenhagen, and they do provide very definite help to the clinician in deciding this important point.

Indications for Dialysis

DR. KARK: Dr. Kolff, you said there were 185 artificial kidneys in this country. Before you came along, there were none, and yet all patients with renal failure did not die. I wonder if you would say something about the use of these units. When should one use the artificial kidney in a patient with acute renal failure? Is there a danger in its widespread use in persons who may recover without such treatment?

DR. KOLFF: A few years ago, papers appeared and addresses were given at meetings such as this by clinicians who had treated, let us say, 12 patients in acute renal failure and had lost only two, and the conclusion was reached that the artificial kidney was not necessary, that patients would recover quite well without the use of dialysis. On the other hand, I was extremely apprehensive that sooner or later people would say that Kolff is a maniac, he treats with dialysis everything but the common cold; and I bent over backward and treated patients with the artificial kidney when the blood urea was higher than 400 mg. per cent, when the potassium was higher than 7, when the alkali reserve was lower than 12, and when the patient was obviously going to die. That meant that even if these chemical values were as I have just mentioned, I would still wait; and we have learned that patients in uremia will die suddenly without giving you the benefit of letting you know beforehand. Everything looks all right, and the next thing you know the nurse says the patient is dead. We still do not know why they die, and that is a very strong argument for dialysis. Do not wait when there is profound uremia.

I recall having seen a report of some 40 cases collected from the literature and an analysis of the deaths, all with acute renal failure, and there were some patients who died

from potassium intoxication. Well, the author of the report said, "That's no reason for dialysis. We have the potassium-binding resins, we can treat them now." There were patients who died from thromboses and emboli in the lung. He said, "The artificial kidney isn't going to cure that." Then there were patients who died from peritonitis or myocardial infarction. "Well, you should not treat that with the artificial kidney." Our thinking is completely reversed now. If we have a patient who has thrombosis, pulmonary embolism, peritonitis and uremia, we treat him; we cannot do very much about the other things, but we can do something about the uremia. It has been amazing to see how, for example, a patient who is comatose due to hepatic failure improves. We dialyze him because we think the uremia may have something to do with it, and the next morning he is sitting up in bed and eating breakfast. If the uremia plays a part in a very severe picture, whether it is the result of an accident or an operation, peritonitis or something else, treat that part of the syndrome that you can treat; that is, treat the uremia.

Every year or so there used to be a paper published about the conservative management of uremia. These papers have disappeared. Have you seen one recently, Dr. Kark?

DR. KARK: No, not recently.

DR. KOLFF: If anyone of you sees a paper like this, please send it to me. These papers were written by people who had no personal experience with dialysis, who had never seen the enormous change in a patient—the reversal of the condition in a patient who is potentially recoverable and who comes in comatose, blue, trying to breathe.

DR. KARK: Thank you, Dr. Kolff. You certainly changed the picture. I think we all agree nowadays that we should start dialysis much earlier and not wait until the patient is almost moribund to try and get him well again.

Chronic Renal Failure

We should say something about chronic renal failure. Patients who have chronic renal failure gradually die, but in this process of dying one sometimes finds ups and downs. The patient may get a second reinfection somewhere and the renal function becomes worse. Dr. Kolff, how do you treat such a patient?

DR. KOLFF: I can tell you that best perhaps by describing a case. The patient, a woman, was known to have chronic renal failure. I saw her for the first time when she was comatose. She had had a convulsion. We treated her with the artificial kidney. A single treatment sufficed to bring her back to a reasonable state. She was able to eat and drink and do the things that you have heard from the other panelists that such a patient should do. She went back to her family, and got along well for about four months. Then she had a repetition of the episode, and we tried again and failed.

I am in favor of giving patients with polycystic kidneys at least one chance. A patient with polycystic kidneys who was brought in with what is called terminal renal failure and the friction rub of pericarditis, a rather severe sign, was treated with three dialyses. The first is to save the patient's life, the second is to bring him into a good clinical condition, and the third, as we hopefully say, is to consolidate the results. How long this consolidation will last, nobody can tell. We find that about one-third to one-half of the patients referred to us with severe uremia on the basis of chronic renal failure are able to go home and maintain some kind of balance for some time.

DR. KARK: Dr. Beattie, what about new kidneys for old?

DR. BEATTIE: I think everybody should have an identical twin, Dr. Kark, if he is going to have renal disease. Until we solve the tissue transplantation problem, kidney transplants will not benefit the majority of our patients. Technically it is not difficult to transplant kidneys with good results. In almost all surgical laboratories in the country, there are surgeons who are adept at moving dogs' kidneys down in the pelves and having them work. We have had our residents practicing it for some years, but we are still waiting for the answer to the transplantation problem, unfortunately.

DR. KARK: Are there any new experimental wrinkles that you have heard of recently?

DR. BEATTIE: We had a little information

TABLE 1

EXAMPLES OF THE REQUIREMENTS FOR A SYNTHETIC NORMAL DIET

Calories	Basal plus 40 per cent
Amino acids*	13 per cent of calories
Emulsified fat†	30 per cent of calories
Glucose	57 per cent of calories
Potassium	121 mEq. (4.7 gm.)
Sodium	243 mEq. (5.6 gm.)
Chloride	220 mEq. (7.8 gm.)
Calcium	1.00 gm.
Phosphorus	1.50 gm.
Magnesium	0.50 gm.
Vitamin A	8300 units
Vitamin D	1600 units
Thiamine	1.6 mg.
Riboflavin	1.3 mg.
Niacinamide	8.3 mg.
Ascorbic acid	50 mg.

*AMIGEN® or LONALAC® (low sodium) may be used.

†LIPOMUL® has been used frequently.

Note: If diet is fed for more than a few days, iodine (Lugol's solution) and iron should be added.

about bone marrow transplantation. If this worked and we could block some of the reactions, we might get somewhere. This is a problem that we have worked on a good deal in our own laboratories. Drs. Monroe, Andresen and Haas have been trying to study some of the problems in transplantation. Pregnant animals accept homologous tissue better than do nonpregnant animals. This has limited clinical application.

Multiple small transfusions do give some beneficial effects. If you attach animals into symbiotic pairs, while the animals are in pairs they will accept cross homologous transplantations better than average; presumably their antibody systems are already being somewhat neutralized by the symbiosis. Once you detach them they are apparently sensitized; subsequent cross transplantations after detachment are rejected at an accelerated rate. There is a good deal of work going on in this field and I think it can be solved. When it is, we will be in the golden era of surgery. There will be no limit to what we can replant.

DR. KARK: Thank you, Dr. Beattie. Dr. Kolff treats chronic renal failure with the artificial kidney when it is needed. Dr. Beattie unfortunately can transplant kidneys only in identical twins. Dr. Pollak, do you have another wrinkle for treating chronic renal failure and tiding the patients over a long period of infection or other cause for the failure?

DR. POLLAK: The problem of treating chronic renal failure frequently is very difficult from a practical point of view. I think the thing we have to remember is that the flexibility of the kidney is gone, to a greater or lesser extent—often almost completely. Consequently it cannot handle very readily all sorts of metabolic end products. One thing it frequently cannot do well is handle sodium normally; it tends to lose rather than retain sodium. Everyone knows that patients with the nephrotic syndrome tend to retain sodium, and everyone tends to restrict the dietary sodium. It appears to us to be not as well known that patients with chronic renal failure without edema frequently *lose* greater or lesser amounts of sodium. If, as often happens, these patients are placed on low-sodium diets, the daily excretion of sodium in the urine will exceed the dietary intake. Over a period of time, sodium depletion becomes severe and this leads to worsening of the renal failure, further elevation of the nonprotein nitrogen, and so on. When this occurs, it frequently can be corrected by giving sodium chloride with sodium lactate in the proper proportions.

Synthetic diets—There are a number of ways one can approach the treatment of chronic renal failure. One which we have used, not having had an artificial kidney available, is by feeding the patient synthetic diets. One of the problems in treating chronic renal failure is simply that of substituting therapeutically for what the kidney cannot do. If the kidney is excreting excess sodium, one has to give the patient an excess of sodium; if the kidney is excreting an excess of potassium, one has to give an excess of potassium; if the kidney is unable to excrete phosphate, one must either reduce the phosphate content of the diet or minimize phosphate absorption by giving aluminum hydroxide by mouth. One way to do this in the hospital is to feed a synthetic diet over a short period by Mead Johnson tube

through the nose and with a pump to administer the food continuously but slowly. The continuous pump is used because these patients tend to become nauseated by synthetic diets if they take them by mouth, and frequently they cannot take nutrients in large amounts, and this way the diet is given very slowly throughout the 24 hours. One can regulate very accurately the type of food given. One can regulate the protein, carbohydrate and fat—and the minerals, perhaps the most important thing of all.

The type of feeding we give in the normal situation is shown in table 1. For the patient with renal failure, of course, one cuts down very substantially on the amount of protein in the diet. We usually reduce it to 0.5 gm. per kilogram, but in certain situations we may lower it temporarily to almost zero.

What can one do with electrolytes in this situation? One can lower the phosphates to zero temporarily, give the patient as much calcium and as much or as little sodium as one wishes, and can tailor the diet to the patient's condition. Over a period of a few days this frequently can be a very effective measure to correct some of the electrolytic derangements in chronic renal failure.

DR. KARK: Thank you for showing us that very simple type of apparatus for long-term care of patients with chronic renal failure. But nobody said anything about potassium deficiency and potassium poisoning. Dr. Kolff, would you like to say something about potassium poisoning?

DR. KOLFF: First I want to disagree a little bit with Dr. Pollak. I think that all the investigations that have tried to prove that you need as much protein as he just expressed are not quite right. I think that if the caloric requirements are covered, the patient can get along with 20 gm. of protein per day indefinitely without developing any protein deficiency, but this is true only if his caloric requirements are covered. If they are not, he will break down his body protein and will lose more and more.

"*Antipotassium cocktail*"—A number of patients with acute renal failure will die in potassium intoxication, and since an artificial kidney is not available everywhere I think it would be a good idea to keep the "antipotassium cocktail" in mind. Let us say you have a patient with impending potassium intoxication. The serum potassium measures 8 mEq. per liter. Some patients are dead before they reach that level. The electrocardiographic changes that are characteristic of potassium intoxication (the high T wave, especially in T II) are evident. If you immediately give such a patient a slow drip of 1 l. of 15 per cent glucose in saline and 180 mEq. of sodium lactate and 10 ampules (10 gm.) of calcium gluconate—whether or not you give insulin does not matter very much—you can almost immediately reverse the electrocardiographic changes. You keep this infusion going in the ambulance until the patient reaches a place where he can be taken care of.

You can also give potassium-binding resin, if you have it. You have a choice between the carboxylic resin and the polyester sulfonate. The carboxylic resin is made by Eli Lilly and Company, and the polyester sulfonate is made by Winthrop Laboratories. The dose of each is 20 gm. at a time, and the 24 hour dosage is about 60 gm., either by mouth or as an enema. By this means one can maintain the potassium within reasonable limits. In fact, one often can control the potassium quite well, so that the potassium level itself is no longer an indication for treatment with the artificial kidney.

DR. KARK: We have heard that patients with acute and chronic renal failure do much better with modern methods of treatment than they did 10 years ago, but we need to be absolutely certain about what we are doing before we start treating them very vigorously. If they need vigorous treatment, it should be given by the right hands in the right manner.

SCIENTIFIC EXHIBIT

Antibiotic Selection in Cutaneous Pyogenic Infections

HARRY M. ROBINSON, JR.

RAYMOND C. V. ROBINSON

JOAN RASKIN

Division of Dermatology, University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, Maryland

This exhibit summarizes 10 years' experience with antibiotics in the treatment of 5000 patients with pyogenic infections and emphasizes the importance of proper selection of drugs.

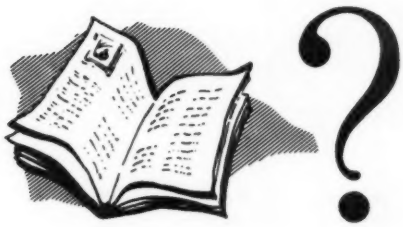
It is impossible to predict the development of a hypersensitive state, but the number of serious adverse reactions may be reduced by using antibiotics only where specifically indicated.

Antibiotic therapy, both local and systemic, has produced severe urticaria, erythema multiforme, exfoliative dermatitis, blood dyscrasias and other adverse reactions.

Adapted from an exhibit presented at the annual meeting of the American Medical Association, Atlantic City.

AVAILABLE METHODS OF ANTIBIOTIC SELECTION

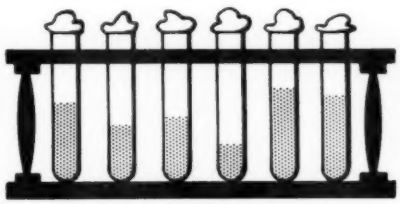
EMPIRIC



JOURNAL GUESSWORK

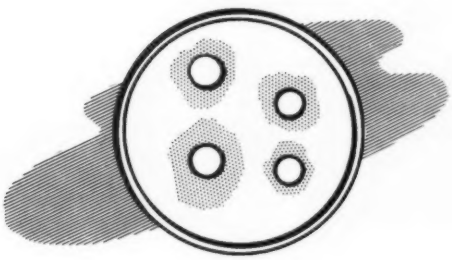
Selection should be based on the published reports of experienced investigators.

TUBE DILUTION SENSITIVITY



1. An accurate *quantitative* method of drug selection
2. Requires well-equipped laboratory and experienced technician
3. More closely approximates the natural environment of the organisms tested

DISK SENSITIVITY



1. A reasonably accurate *qualitative* method of drug selection
2. Minimum of equipment required
3. Commercially manufactured antibiotic disks may lose their potency in shipping and storage.

SENSITIVITY TESTS SHOULD BE PERFORMED ON ALL CULTURED ISOLATES

DISEASE	ORGANISMS MOST FREQUENTLY CULTURED	METHOD OF ESTABLISHING DIAGNOSIS	METHOD OF SELECTING ANTIBIOTIC	M ADM AN
Pustular folliculitis Few to numerous papules and pustules, originating in the hair follicles of the buttocks, thighs, trunk and scalp	*Staphylococcus aureus* *Staph. albus*	Clinical and morphologic characteristics and culture	1. Empiric 2. Disk or tub dilution sensitivity	Topi or bo
Furunculosis and carbunculosis A furuncle is an extensive pyogenic infection involving a single hair follicle. Carbuncles are deep-seated conglomerate furuncles with multiple openings.	*Staph. aureus* *Staph. albus*	Clinical and morphologic characteristics and culture	1. Empiric 2. Disk or tub dilution sensitivity	Topi syste
Erysipelas Sharply demarcated, bright red, edematous, shiny lesion. Surface may be covered with small vesicles. Systemic symptoms include fever, malaise and lymphadenopathy.	*Streptococcus pyogenes*	Clinical and morphologic characteristics and culture	Primarily empiric	Syste
Cellulitis and lymphangitis Cellulitis is a localized interstitial infection of the skin and subcutaneous tissue. Patient may have systemic symptoms. Lymphangitis is manifested by red streaks along inflamed lymph vessels.	*Str. pyogenes*	Clinical and morphologic characteristics and culture of exudate	1. Empiric 2. Disk or tub dilution sensitivity	Syste
Pustular and cystic acne A severe form of acne vulgaris in which large pustules and cystic lesions may be followed by extensive formation of scars	Staphylococci may be isolated, but etiologic significance is uncertain.	Clinical and morphologic characteristics	Empiric	Syste
Impetigo contagiosa Superficial, thin-walled vesicles and vesicopustules which rupture easily, forming crusted lesions. These heal without formation of scars. Very contagious and autoinoculable	*Staph. aureus* *Str. pyogenes*	Clinical picture is characteristic. Cultures are of academic interest only.	Empiric	Top
Ecthyma (deep-seated impetigo) Pyogenic lesions of the extremities, genitalia and trunk which form ulcers. Healing is accompanied by formation of scars.	*Staph. aureus* *Str. pyogenes*	Clinical picture is characteristic. Culture is necessary in resistant lesions only.	Empiric	Top Occa requ thera
Dermatoses complicated by secondary pyogenic infection Pyogenic bacteria are inoculated by scratching pruritic eruptions such as eczema or papular urticaria.	*Staph. aureus* *Str. pyogenes*	History, physical examination, and culture	Empiric	Top Occa requ ther

METHOD OF ADMINISTERING ANTIBIOTIC	ANTIBIOTIC OF CHOICE			DOSAGE SCHEDULE	
	Drug	Number of patients	Number of satisfactory results	Adults	Children
Topical or systemic, or both	Triacetyloleandomycin	16	14	1 gm. daily in divided doses	50 mg. per kilogram daily in divided doses
	Erythromycin	31	23		
	Novobiocin	11	8		
	Chloramphenicol	14	13		
Topical and systemic	Triacetyloleandomycin	31	31	1 to 2 gm. daily in divided doses	50 mg. per kilogram daily in divided doses
	Novobiocin	15	15		
	Chloramphenicol	20	16		
	Erythromycin	23	21		
Systemic	1. Penicillin	10	9	1. 1.2 million units BICILLIN®	1. 600,000 units Bicillin
	2. Chloramphenicol	5	5	2. 2 gm. daily in divided doses	2. 50 mg. per kilogram daily in divided doses
	3. Triacetyloleandomycin	2	2	3.	3.
	4. Erythromycin	3	3	4.	4.
	5. Tetracyclines	2	2	5.	5.
Systemic	1. Penicillin	15	13	1. 1.2 million units Bicillin	1. 600,000 units Bicillin
	2. Triacetyloleandomycin	15	15	2. 2 gm. daily in divided doses	2. 50 mg. per kilogram daily in divided doses
	3. Tetracyclines	45	40	3.	3.
	4. Erythromycin	48	45	4.	4.
	5. Chloramphenicol	28	25	5.	5.
Systemic	Tetracyclines	196	161 temporarily benefited	Initial dose 1 gm. daily in divided doses Maintenance dose 250 to 500 mg. daily	Not to be used in children for this condition
Topical	Ointments and lotions containing neomycin, gramicidin and bacitracin	628	627	Systemic therapy unnecessary	
Topical Occasionally requires systemic therapy		342	340	If lymphangitis develops, systemic therapy will be necessary.	
Topical Occasionally requires systemic therapy	The available steroid-antibiotic ointments and lotions are usually effective.	280	266		

ANTIBIOTIC THERAPY OF STAPHYLOCOCCIC INFECTIONS

(Summary based on 10 years' experience)

DRUG	AVAILABLE FORMS	EFFECTIVENESS	REACTIONS				
			Incidence	Gastrointestinal	Blood	Skin	Sensitizing potential
Triacetyloleandomycin	Oral	A	+	m	0	0	0
Erythromycin	Oral	A	+	m	0	0	0
	Local	A	0	0	0	0	0
Chloramphenicol	Oral	A	++	m	s	0	0
	Local	A	+			s	+
Novobiocin	Oral	A	++++	m and s	s	s	++++
Tetracyclines	Oral	B	+++	m and s	0	0	0
	Local	A	0				
Penicillin	Oral	C	++++	m	0	s	++++
	Injectable	C	++++	0	0	s	++++
	Local	A	++++	0	0	s	++++
Neomycin	Local	A	0				0
Gramicidin	Local	A	0				0
Bacitracin	Local	B	+			m	+

m — mild s — severe

CONCLUSIONS

Antibiotic therapy, local or systemic, should be limited to those conditions in which it is specifically indicated.

Empiric therapy of staphylococcic infections with triacetyloleandomycin, erythromycin, novobiocin or chloramphenicol is usually successful. Selection of drugs by the disk diffusion or tube dilution method is necessary in resistant cases.

In superficial pyodermas the bacteria are subjected to overwhelming concentrations of an antibiotic when treated locally and therefore are seldom resistant to therapy.

Program and Results of a Camp for Obese Adolescent Girls

PENELOPE S. PECKOS,* JOHN A. SPARGO† AND FELIX P. HEALD‡

Harvard Medical School, Boston, and Children's Hospital, Washington, D. C.

PENELOPE S. PECKOS

THERE is an abundance of articles in the medical and nutritional literature on the prevalence and treatment of obesity. The effects of obesity on personality and longevity have been well documented by many authorities.[1-4] The treatment of obesity has run the gamut from liquid-formula diets to all-meat diets, as well as a variety of appetite depressants, bulk-producing pills and candies. Furthermore, in recent years, various health salons and weight-reducing centers have appeared and have thrived throughout the country. The percentage of success of any treatment to date has been pitifully small; this fact continues to plague physicians and nutritionists, whether they treat this condition in hospital outpatient departments, private offices or psychiatric clinics.

It appears that obesity is not confined to the adult population alone. It is as prevalent in our adolescent population.[5] Obesity during adolescence merely compounds the stresses and strains that are present normally during this age. For this reason, specific knowledge of adolescence with regard to normal growth, nutrition and psychology is necessary before this condition can be treated successfully. This is a period when these young people, especially the girls, become very conscious of their figures, their appearance and their social success. Physical appearance and social acceptance are closely related in our culture, particularly within this age group. Any obvious disorder, such as obesity, which makes these young people unattractive and not accepted by their peers is very disturbing to them. Since many obese adolescents are socially ostracized and ridiculed, they develop strong feelings of in-

*Nutritionist, Forsyth Dental Infirmary; Instructor in Nutrition, Harvard University School of Public Health; Associate in Public Health Nutrition, Simmons College, Boston, Massachusetts.

†Assistant Physician, Adolescent Unit, Children's Medical Center; Instructor, Harvard Medical School, Boston, Massachusetts.

‡Director, Adolescent Unit, Children's Hospital, Washington, D. C.

FIGURE 1. Main house at Seascape, containing 10 bedrooms and recreational and dining facilities.

feriority, which are manifested adversely in their school work, personalities and attitudes. In their desperate attempt to remedy their obesity, they resort to bizarre eating habits which are unsound nutritionally (poor in proteins and vitamins) at a time when their growth demands optimal nutrition. The resultant diet is usually not conducive to weight loss, and discouragement over failure to lose weight adds further misery to an already unhappy situation.

Because of these factors, Camp Seascape was founded in the summer of 1959. Its purpose was to provide an eight week medically oriented program for reducing obese adolescent girls. The program was designed to include nutrition re-education and a discussion of some of the factors responsible for obesity, with the hope that these girls would be able to control their weight in the future. We believe that some of the reasons for the lack of success of reducing programs in outpatient situations are that (1) environmental factors cannot be controlled, (2) nutritional re-education of the patient cannot be fully achieved due to lack of time, and (3) new interests and physical activities cannot be provided. It is apparent that these conditions are essential to the success of any weight-reducing program, particularly for adolescent girls. Further research may indicate single or multiple physiologic defects in metabolism which have as a common result the excess storage of fat. Meanwhile, the empiric approach to the problem of weight reduction is reducing food intake or increasing energy expenditure through consistent physical activity, or both. The difficulties which outpatients have in adhering to such measures make us feel that removal of the individual from the home to a less emotionally charged environment with complete nutritional control and re-education would be more successful in achieving permanent weight loss.

Plant, Subjects and Program

The camp property is essentially an estate comprising 20 acres of land, two large buildings, and 750 ft. of sandy beach front, located

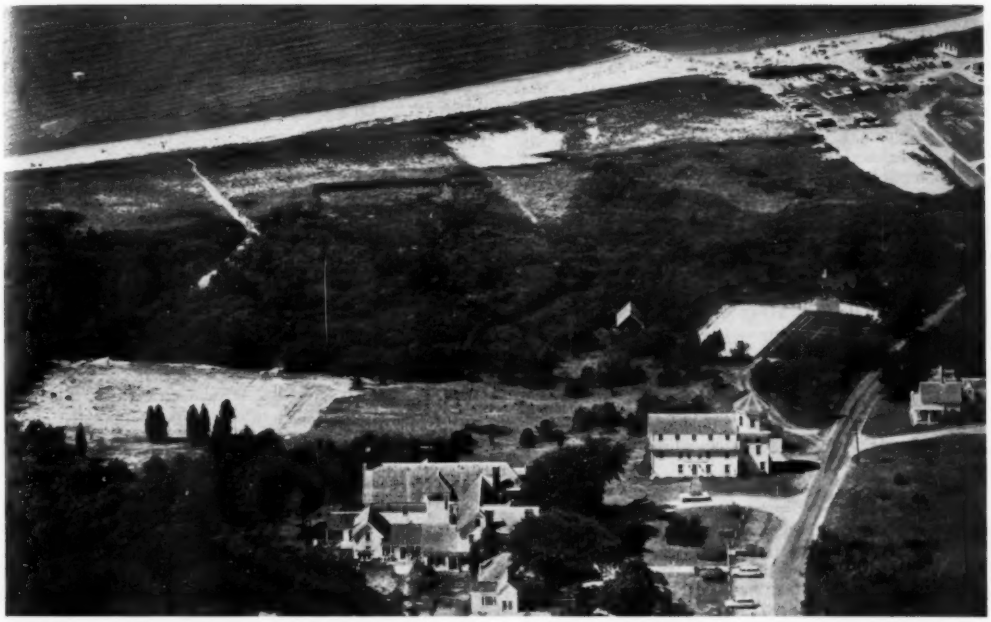


FIGURE 2. Aerial view of Seascape, showing main house in the foreground, beach house at right rear, and play facilities and beach in the background.

on the bay side of Cape Cod in the town of East Brewster, Massachusetts. One of the buildings is a luxurious main house of 15 rooms, including two large living rooms, two dining rooms, large kitchen and 10 large bedrooms. The second building is a beach house done in a rustic knotty pine motif, containing 25 double-occupancy bedrooms and a large central living room (figures 1 and 2). This environment was considered far better for the purposes of this camp than the conventional bunk-type arrangement of the ordinary summer camp. All facilities necessary for a comprehensive camp program were provided.

Thirty-eight campers were enrolled, most of them for eight weeks, some for four weeks, and a few for two or three weeks. Age range was 12 to 21 years, the majority falling in the 14 through 16 year group. Weight ranged from 145 to 284 lb., the average being 189 lb.

Our present knowledge of obesity and nutrition in the adolescent suggested that the diet should be high protein, moderate fat and low carbohydrate. The protein intake was about 8 oz. per day, all from animal sources and most of it being meat. Extra protein was obtained from eggs three to four times per week. The fat intake was not actually calculated. All visible meat fat was trimmed before cooking; small amounts of oil (WESSON®) were used in cooking and in salad dressing, and one pat of butter (108 squares per pound) was allowed at breakfast if toast was served. The carbohydrate intake was low; one slice of toast or a small bowl (one cup) of dry cereal was given at breakfast, and four saltines were allowed three to four times per week as a bedtime snack. Natural carbohydrates were, of course, obtained from vegetables and fruits. A sample menu is shown in table 1. The average number of calories per day was 1200, varying from 1100 to 1,350, depending on the menu. The diet was well received and apparently satisfying, for we had no complaints about the food, which was rather interesting.

The activity of the campers was planned so that they could elect two or more areas daily in which they had a particular interest.

TABLE 1

SAMPLE MENU AT SEASCAPE

BREAKFAST

4 oz. orange juice
1 scrambled egg
1 slice enriched toast
1 small pat butter
8 oz. skim milk

LUNCH

1 cup shrimp salad on lettuce leaf
3 slices tomato
2 celery stalks
1/10 honeydew melon
8 oz. skim milk

DINNER

4 oz. roast beef *au jus*
½ cup peas
2 cups (approximately) tossed green salad
4 oz. ice milk
8 oz. skim milk

Snacks were distributed four times per week before bedtime and consisted of a fresh fruit (peach or plum) or 2 pieces Melba toast or 4 saltines.

TABLE 2

REPRESENTATIVE DAILY* SCHEDULE

TIME	ACTIVITY
A.M.	
7:00	Reveille
7:30	Breakfast
8:00	Sick call
8:15	Room and beach house cleanup
8:45	Inspection of beach house
9:00-12:00	Morning program†
	First period: elective activity (chosen daily)
	Second period: swimming and boating
P.M.	
12:30	Lunch
1:15	Rest period
2:15-5:00	Afternoon program
	Third period: achievement (chosen for one week)
	Fourth period: games and sports
5:15	Free period (unscheduled time)
6:00	Dinner
7:00-bedtime‡	Varied activities, including theater, bowling and excursions, or free time

*Sunday program was flexible to permit attendance at church.

†Periods rotated with the tide. Activities included archery, bicycling, swimming, sailing, water skiing, horseback riding, instruction in fashion and cosmetics, tennis, badminton, volleyball, dancing (square, modern and interpretive), golf, rowing, arts and crafts, painting and nature study.

‡Bedtime was determined according to age of camper.

Swimming and games were compulsory for all campers. The negative reaction by the campers to certain physical activities was interesting, and will be discussed later. A typical day's schedule is shown in table 2.

The educational program was considered one of the most important aspects of the camp. It consisted of a series of discussions on nutrition given by the nutritionist. These talks covered the basic four food groups and their nutrients; amounts recommended for age groups; food fads and fallacies; how to choose foods in any situation such as a party, going out to dinner, etc.; and making proper substitutions. The girls were divided into two age groups, 12 to 15 years and 16 to 21 years, and discussions were held three times per week. Individual conferences were also scheduled daily so that personal problems regarding nutrition and related subjects could be discussed. Each girl was seen three or four times at a private conference during the summer apart from daily contact.

The medical aspects of the program were handled by the camp director, a pediatrician who works exclusively with adolescents. He, too, had private conferences with each girl throughout the summer to help her with any problems, whether medical, social or psychologic. Sick call was held in the infirmary three times daily, once after each meal. The fact that this was too well attended will be elaborated further.

Group therapy sessions were conducted weekly by the medical consultant (Dr. Heald). They were helpful for the girls, as well as useful for the staff in understanding the problems of the campers. As a result of these sessions, the girls were able to discuss for the first time and with each other many of their feelings about obesity.

Other aspects of the educational program included art instruction by an accredited art teacher once a week, arts and crafts daily, and theater every week; an adequate reading and music library also was provided. All phases of

good grooming were covered by the staff and by visiting hair stylists, beauticians and fashion experts.

The advantages of the camp were twofold: (1) The girls were brought together in a pleasant setting under the supervision of professional personnel for an eight week period, and (2) the opportunity was provided under these conditions to re-educate them about diet and food habits and to stimulate and encourage new general interests and physical activity.

Results

The results of this program were very gratifying. All campers lost weight. The smallest weight loss was 8 lb.; this girl was a diabetic. The greatest weight loss was 38 lb. The average loss was 22 lb. per camper over the eight week session.

Rate of weight loss per week varied among the girls and in the individual girl, as might be expected. Some girls lost as much as 7 lb. per week, while others lost 1 to 4 lb. per week. For this reason and because the girls tended to compare number of pounds lost with each other, the staff minimized the importance of actual pounds lost. Instead, the staff stressed the individual differences in body build among the girls and their decrease in measurements and dress size, which was considerable in many instances.

The other important result of the program was the tremendous improvement in personality in almost all the girls. This was noticeable to the staff as well as to the parents, even after the first month of camp. The changes were manifested in various ways—their ability to adjust to group living, their desire to make and maintain friends, and their confidence in being accepted as members of society for what they were and not what others wanted them to be. Several girls who had had no desire to enter college decided to apply midway through the season, and they were accepted by the schools of their choice. Many of the girls acquired new interests, some in art, others in various sports such as water skiing, sailing, tennis, folk dancing, and, strangely enough, physical fitness (exercises). Some of the girls who were quite withdrawn initially developed a social awareness that helped them to enjoy their stay and to make many friends. As an example of their social development, the campers arranged a midwinter reunion so that they could renew friendships and compare progress notes.

Discussion

A review of the summer indicates that the general success of the camp's first season was due to a combination of several factors; no single reason can be given all the credit.

The staff felt that the association of the campers with mature "accepting" young adults, the establishment of good interpersonal relations, and the complete change of environment for a prolonged period combined to produce an atmosphere of security as well as understanding. Some other factors that helped were (1) controlled food intake; (2) the fact that all the girls had the same problem to solve to a greater or lesser degree; (3) the therapeutic value of group discussions among the girls, with and without staff; and (4) the therapeutic value of weigh-in day once a week, which motivated the girls to compete with their friends and with themselves to achieve maximal weight loss.

It is well known that obese adolescent girls are sedentary and noncompetitive by nature.[6] One of the biggest problems that the staff encountered was motivating the girls to acquire an interest in physical activity. Some inertia in these girls was anticipated, but the tremendous amount found in this group was surprising to the staff. The activity schedule was, therefore, very conservative during the first two or three weeks of the season. Even swimming, which is usually enjoyed by all age groups (whether lean or heavy), was shunned by a good number of the campers. The other most disliked activity was games in which teams had to be chosen and competition was expected. Interestingly enough, these two activities were made compulsory by the camp staff for all the girls, and even now it is difficult to determine how much of the campers' resistance was due to adolescent rebellion and how much was due to their innate noncompetitive nature.

Once the campers were secure in their relationship to the camp staff and to their counselors, the activity program was stepped up, and the girls participated and developed skills in the various activities that they had initially resisted. The counselors were a very important stimulus to the campers in motivating them to develop an interest in physical activity. These counselors were carefully chosen for their abilities in the various activities, as well as for their individual attributes and personalities. These girls lived with the campers. It was important for them to have some comprehension of the problems of obese girls and some ability to handle with understanding and sympathy the little crises that arose in the dormitory. It can be said that they constituted the nucleus of the camp staff and were *vital* to the success of the program.

The activities that the girls enjoyed most were noncompetitive, as one might expect. These included archery, modern and folk dancing, sailing, water skiing, horseback riding, tennis and badminton.

Much to our surprise, the diet was received extremely well. The campers eagerly awaited each meal, and generally speaking, there were very few complaints about the food. Some strong food dislikes, an allergy, and several food taboos were honored; otherwise, no substitutions were permitted at any meal.

The foods served to the campers were the common varieties available in the Northeast. Dietetic foods were not used, except for powdered skim milk, SUCARYL® and a form of low-caloric ice cream. It is the philosophy of the staff that the campers should be taught to eat the essential foods in proper amounts in any environment. Parents cannot be expected to maintain a separate kitchen for a dieter, even if the economics of the family permit it. Furthermore, this would give the obese adolescent one more reason for feeling abnormal and different, which, in turn, would discourage her from continuing a diet.

The meals were served by waitresses; although campers, counselors and staff could come to breakfast and lunch in sportswear, all camp personnel were required to dress for dinner. The reason for this was obvious. These girls were extremely untidy about their appearance and personal affairs, and good grooming was part of the educational program. Rebellion toward this rule was evident initially, but toward the end of camp, the girls had developed a sense of pride in their appearance and were eager to look their best.

The initial withdrawal of food evoked a strong reaction among the girls. Mild to moderate depression was general, and there was a fair amount of uncooperativeness and hostility for a period of about one week after the beginning of camp. We related this to the withdrawal of food, and wondered if this is one reason why so many people cannot remain on diets voluntarily. Oral gratification seemed to be needed and this was manifested by an unusual amount of gum chewing. It was decided to permit this on camp property, but the girls were asked to abstain when in public. There was a noticeable decrease in the frequency of gum chewing by the end of the camp season.

The rate of hypochondriasis was very high, and sick call was one of the most popular events of the day. It was extremely well attended; usually, 5 to 12 girls would appear after each meal. The complaints were generally of minor importance, such as mosquito bites, poison ivy and dysmenorrhea. The medical staff believed that this was primarily an attention-getting device; therefore, it was tolerated and handled gently. The number of visits to the camp physician was very high when contrasted to that of the ordinary camp. The number of visits to the infirmary decreased toward the end of the camp season.

There was a very obvious change in the attitude and behavior of the campers by the time camp closed. The noisy, boisterous girls were more quiet; the withdrawn girls were more sociable and friendly, and the appearance of all the girls was much improved. They were several dress sizes smaller and, therefore, more attractive and neater; they were very happy with their accomplishment. These are important reasons for the change in attitude and personality that was observed in the campers.

A seminar was held for the parents on the morning of the last day at camp to discuss the

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various aspects of the camp program. The medical and psychologic aspects of obesity were discussed by the medical staff, and the dietary aspects were discussed by the nutritionist. Discharge diets were made out for each camper, and a follow-up program was evolved at the request of the campers.

Since the majority of the campers were from New York and Boston, two groups were formed. Each group was to meet once a month in each city with the staff so that any problems regarding continued weight loss and weight control might be discussed. This is an important feature of the camp program, since it permits the staff to continue the supervision of the girls and provides an opportunity to evaluate the educational program more accurately for future camp seasons.

Two such follow-up meetings were held while this paper was being written, and it is gratifying to report that the girls who attended have continued either to lose weight or to maintain their weight.

All the girls will be contacted yearly until maturity is reached so that longitudinal data regarding their progress may be obtained and evaluated.

Summary

Camp Seascape, located on Cape Cod, was founded for the purpose of providing an eight week medically oriented summer program for reducing obese adolescent girls. The program was designed to include nutrition re-education and to provide new interests and physical activities. Discussions on nutrition and some of the factors responsible for obesity were included with the hope that these girls would be able to control their weight in the future. Good grooming and other aspects of appearance were stressed.

Thirty-eight campers were enrolled, ages 12 to 21. Weight ranged from 145 to 284 lb. The diet provided for the campers was high protein, moderate fat and low carbohydrate, containing an average of 1200 calories.

The medical aspects of the camp were handled by the camp director, a pediatrician, who works with adolescents exclusively. Initially, the rate of hypochondriasis was high, mild to moderate depression was evident due to the withdrawal of food, the degree of inertia was high, and many of the girls were either very boisterous or very withdrawn.

The results were very gratifying. All campers lost weight, the average loss being 22 lb. per camper. The rate of hypochondriasis decreased considerably, the depression disappeared, and the boisterous girls quieted down while the withdrawn girls developed a social awareness that permitted them to make many friends. The girls became very active, developed skills in various activities, and were generally very pleased with their accomplishments and their appearance.

Monthly follow-up meetings were suggested by the campers. At two such meetings, all the girls who attended had either continued weight loss or had maintained the weight attained at the camp.

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CLINICOPATHOLOGIC CONFERENCE

Report From Veterans Administration Hospital, Hines, Illinois

Edited by William J. Gillesby, M.D., Assistant Chief, Surgical Service

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Case Report

First admission—A 54 year old woman was hospitalized in Hines Veterans Administration Hospital on April 4, 1950. She complained of menorrhagia and prolonged menstruation of 7 to 10 months' duration, with pinkish discharge between periods and episodes of vaginal bleeding and blood clots.

Examination showed a necrotic fibroid polyp protruding from the external os. The vagina was removed and the pathologic report was polypoid adenomyoma. The patient was discharged on May 2, 1950.

Second admission—On December 26, 1951, the patient was readmitted to Hines with symptoms of peptic ulcer of one year's duration. Gastrointestinal x-rays showed negative findings, and the symptoms subsided with medical management. The patient recalled that she also had had some abdominal pain during her previous hospitalization at Hines. She was hospitalized until January 26, 1952.

Third admission—The patient was again admitted to Hines on April 6, 1953, complaining that she had had vaginal bleeding for the past six months. Dilatation and curettage were done; later, a panhysterosalpingo-oophorectomy and appendectomy were performed because of a papilliferous carcinoma of the uterus. A tumor was found at the entrance of the left fallopian tube.

The patient was discharged on April 17, 1953. Re-examination on December 22, 1953, June 22, 1954, and December 20, 1954, showed no recurrence of the lesion.

Fourth admission—The patient was admitted on March 11, 1956, because of urinary frequency, nocturia, pyuria and hematuria of about one year's duration. Results of an intravenous pyelogram were negative. Cystoscopy revealed a tumorlike mass at the trigone of the bladder which seemed to involve the right ureteral orifice. Biopsy showed a grade 4 transitional-cell carcinoma. A total cystectomy was done and the ureters were implanted into the rectosigmoid. Hydronephrosis developed on the right side, and lysis of adhesions of the right ureter was done. Adhesions had caused angulation of the ureter at the anastomosis.

The patient was discharged on May 22, 1956. Follow-up intravenous pyelograms on November 20, 1956, and May 18, 1957, showed prompt excretion bilaterally. The pelvis and calyxes of the right kidney were dilated and irregular in outline. Manual examination showed no recurrence of the tumor.

An intravenous pyelogram on December 20,

1957, showed prompt bilateral excretion. There was nonvisualization of the calyceal system on the right, with an irregular collection of opaque material in the region of the right kidney, which probably was the result of hydronephrosis due to obstruction of the right ureter.

Final admission—The patient was admitted to Hines for the last time on April 26, 1958. During the preceding few months, she had had occasional bouts of pain in the abdomen and right flank which were associated with nausea and vomiting. The symptoms usually disappeared spontaneously. The episode which led to hospitalization lasted six days and did not subside. The patient had had anorexia during the few weeks prior to admission.

While serving in the Women's Army Auxiliary Corps in the Philippine Islands and the South Pacific from 1943 to 1945, the patient had had malaria and dengue. Her history also showed that both her grandmother and her mother had had hysterectomies for carcinoma of the uterus.

Physical examination—At the time of admission, physical examination showed that the patient was thin but well developed. She was acutely ill and in distress, and was holding her right hip and knee flexed. Blood pressure was not recorded at this time; temperature was 98° F., and pulse was 108. There were no masses in the breasts and the lungs were clear. The heart was not enlarged and no murmurs were noted. The abdomen was diffusely tender bilaterally, with slight distention. No masses were felt on bimanual palpation. Cough rebound was referred to the right flank and groin. The right costovertebral angle was extremely tender. Bowel sounds were of normal quality but occurred infrequently. There was a slight whitish discharge from the vagina, but an examination with a speculum gave negative findings. Rectal examination was negative, and the genitalia were atrophied. There was no evidence of recurrence of tumor in the uterus or bladder.

Hospital course—Free air studies on April 27 gave negative results. The roentgenologist reported the presence of air in the small bowel and in the colon, including the sigmoid and rectum. There were multiple air-fluid levels. No dynamic loops were demonstrated among the air-fluid levels. An oval calcific density was noted in the right side of the abdomen; this may have represented a calcified mesenteric node. It was thought that the patient had spastic ileus with possible ascites.

Intravenous pyelography was done on April 28. A preliminary film showed a density in the right upper quadrant which may have represented a calculus. Because the right pelvicalyceal system was not visualized, it was impossible to determine whether the stone was in the gallbladder or of renal origin. The nonvisualization of the right kidney would indicate that it was of renal origin. The left renal pelvis was normal. Although the left calyceal system was poorly visualized because of fecal material, the visualized part of the left ureter was normal.

On April 26, the patient was given fluids, and a Levin tube with continuous suction was introduced. Her condition was improved on April 27, but she was still dehydrated and had pain in the abdomen. She had no nausea. On the following day, her condition was the same. She had had no urinary output since admission; however, the bed was soaked with urine, which the nurse thought was passed through the rectal tube.

The patient lapsed into a coma on the night of April 28. The possibility of hyperchloremic acidosis was considered. At 9:30 P.M. on April 29, her blood pressure was 145/50; at 9:40 P.M., it was 125/20. LEVOPHED® was administered. At 10 P.M. she had three convulsions. Urinary output was 800 cc. in 12 hours. The patient died at 10:50 P.M. on the fourth day of hospitalization.

Laboratory data are summarized in table 1.

Discussion

DR. CHESTER J. GAJEWSKI (clinical associate obstetrician and gynecologist, Stritch School of Medicine of Loyola University, Chicago, and attending gynecologist, Hines Veterans Administration Hospital): This patient, Gravida II Para I, was 46 years old at the time of her first hospitalization at Hines. A physician is somewhat suspicious that a pathologic condition exists in a 46 year old woman

TABLE 1

LABORATORY DATA

TESTS	DATES			
	4/26*	4/27	4/28	4/29
Hematology				
White blood cell count	13,100		9000	3300
Polymorphonuclear cells (per cent)			68	70
Lymphocytes (per cent)			32	27
Monocytes				3
Hemoglobin (grams)	12		11	13
Hematocrit (per cent)	37		39	41
Chemistry				
Nonprotein nitrogen	48		64.6	69.3
Carbon dioxide (milliequivalents)		13.0	8.3	12.6
Chloride (milliequivalents)		102	109	109
Sodium (milliequivalents)			142	133
Potassium (milliequivalents)			2.95	2.50
Complement fixation			Nonreactive	
Urinalysis				
Urine (by rectal tube)			Alkaline	
Specific gravity			1.012	
Albumin			3 plus	
Albumin (mg. per 100 cc.)			50	
White blood cells			4-6	
Red blood cells			Few	

*An electrocardiogram made on April 26 was abnormal. It showed nonspecific ST-T changes and a possible old posterior infarction on the basis of the Q complex in leads II and III and the aVF (augmented unipolar foot) pattern.

who is still menstruating regularly, and when a patient of this age gives a history of a change in the character of the menses, with intermenstrual bleeding, he suspects adenocarcinoma of the endometrium until it is proved otherwise. This is the *sine qua non* in the early diagnosis of this condition. There is no mention in the protocol of any evaluation of this patient's menstrual history, nor is there mention of a complete pelvic examination despite the history.

Two terms which we commonly use are "patient delay" and "physician delay." This patient's history goes back over a three year period; I would estimate that the patient delay would date back to a time seven months prior to her first admission to the hospital. There was a change in the character of her menses; yet, she waited 7 to 10 months to see a physician. In the event of a protrusion from the external os, the polypectomy is performed, of course; however, a dilatation and curettage also should be done. With this patient's history, it is very likely that the beginning of the carcinoma was evident in April 1950, and she should have had a curettage during her first hospitalization. She also should have had a pelvic examination and re-evaluation during her second hospitalization.

A group in Stockholm has done a brilliant evaluation of radiation without surgery as the primary treatment in adenocarcinoma of the uterus. According to this school, radiation alone gives as fine a statistical end result as does radiation plus surgery or surgery alone. On the other hand, there is the school which believes that since this is a slow-growing condition which tends to spread along the surface of the endometrium, through the tubes onto the ovaries, through the cervix onto the vagina and into the cul-de-sac (the so-called droplet metastases) and to penetrate the muscularis of the uterus slowly the patient will be served best and most rapidly by a primary surgical approach. Advocates of this treatment further believe that radium and x-ray play no role in treating this condition, or perhaps they use some x-ray postoperatively just to assure the

patient that everything is being done for her and that she has not been forgotten.

The chances for survival are in the realm of 98 per cent in cases in which the disease is confined to the muscularis of the uterus and has not penetrated beyond the serosa. A simple classification of the extent of the disease is as follows: Disease confined to the endometrium is stage 1; penetration beyond the endometrium, stage 2; penetration to the serosa, stage 3, and penetration through the serosa to some distance, stage 4. There are almost as many classifications as there are surgeons who have operated on patients with this condition, but the foregoing grouping is easy to remember. When the disease is confined entirely to the endometrium as stage 1, preoperative selective treatment with radium should be followed by a six to eight week interval to allow the maximal effects of radiation to subside. Then a total abdominal hysterectomy and bilateral salpingo-oophorectomy of the upper third of the vagina with careful manipulation of the uterus and its appendages should be done. With this approach, a five year cure should be obtained in almost 100 per cent of cases. The disease has an excellent prognosis.

This patient was hospitalized for the fourth time after having had hematuria and pyuria for a year. At this time a Coffey transplantation of the ureters into the rectosigmoid was done. In cases in which it is necessary to transplant the ureters because of a pelvic pathologic condition (whether it is intrinsic to the bladder itself or involves the uterus or its appendages), there has been a recent revival of interest in use of the Wertheim operation and its modifications, in the Wertheim operation with lymphadenectomy, and in the more radical procedures with excision of the bladder or rectum, or both, for extensive carcinoma of the cervix. This has greatly emphasized the problem of the urinary tract-draining structures, the ureters and kidneys.

The simplest procedure to save a kidney or to maintain kidney function probably is a ureterostomy. However, this is a horrible procedure for the patient; urine continually dribbles down the abdominal wall, and no satisfactory apparatus has been designed to collect it. In an attempt to avoid having to perform ureterostomy, efforts have been made to transplant the ureters into the colon. The problem here is immediately apparent. When the urinary stream is directed to the contaminated fecal contents of the rectosigmoid, pyelitis or pyelonephritis may develop. Either of these conditions may become uncontrollable and cause death. Repeated attacks of pyelitis also may produce a deficient or diminished kidney drainage system in which tubular absorption becomes deranged and chlorides are absorbed. As a result, hyperchloremic acidosis develops and the patient dies.

From practical experience, I have found that in order to avoid contamination from the fecal stream, the Bricker pouch is probably the best of the presently used urinary reservoirs. The Gilchrist operation is, of course, a formidable procedure and is rarely, if ever, done in one stage with a radical pelvic exenteration. The construction of the pouch and the mobilization of the cecum are difficult procedures which require a great deal of time. Added to the pelvic operation itself, these procedures make an interminable operation which not many surgeons or patients can stand. If a Gilchrist procedure is used, it usually is done in two stages. Establishing a Bricker pouch is much simpler, and it can be done at the time of original surgery.

I want to mention that a pyelogram is no real index of kidney function. It will show excretion, but it tells nothing of the composition of the urine or of the blood chemistry. Although the kidney is able to excrete urine, we need to know the kind of urine, its specific gravity, and its mineral constituents. We also need to know the patient's blood level of potassium, sodium, chloride, etc. We must have a better evaluation of kidney function than can be obtained from an intravenous pyelogram. I think that this patient would have been benefited by some blood studies in addition to intravenous pyelography.

Sometimes, an enormous stoma will be found at autopsy, and yet the patient will have had very poor kidney function at the site of the ureterostomy. Apparently, a bridging across this stoma to some of the smooth mus-

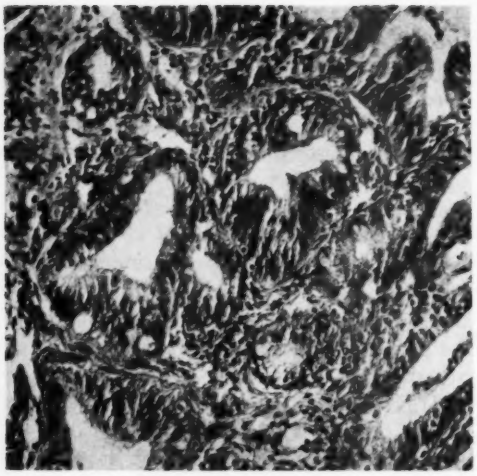

FIGURE 1. Photomicrograph showing endometrial carcinoma of the uterus.

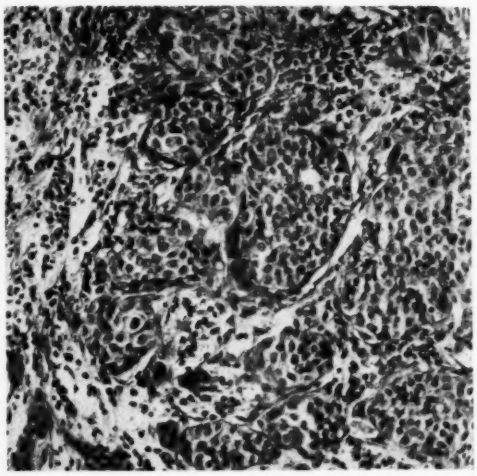

FIGURE 2. Photomicrograph showing transitional-cell carcinoma of the bladder.

cle in the uterus is necessary for a continuous peristalsis. Otherwise, although the stoma may be large and patent, there is not a natural flow of urine, and peristaltic ureteral waves do not push the urine into the bladder; instead, there is a tendency toward stasis infection and deranged tubular absorption. Ultimately, the same effect is produced as if the ureter had been knotted or tied.

On the day of death, this patient had a carbon dioxide level of 12.6 mEq.; the potassium was 2.5 mEq. and chlorides 109 mEq. Nonprotein nitrogen had risen to 69.3. These findings indicate that the Coffey ureteral transplantation into the intact rectosigmoid might not have proved as successful as a ureterostomy would have been. The latter, of course, is an abomination, and perhaps a Bricker pouch or Gilchrist procedure of the isolated cecal loop might have served the patient somewhat better.

There are some who believe that this absorption of chlorides in hyperacidosis comes from the intact intestinal tract, but I think the evidence today favors the theory that absorption of chlorides results from deranged tubular mechanisms in ascending pyelonephritis. Some recent surgery on dogs has shown the possibility of constructing a urinary bladder from a segment of the ileum, with transplantation of the ureters into the urinary reservoir.

DR. WILLIAM E. FREDERICK (assistant chief, radiology service): The first of several intravenous pyelograms of this patient, dated April 9, 1953, showed evidence of some dilatation of the upper calyxes on the right side. The left side was normal after the ureteral sigmoidostomy, and there were no other findings. The right kidney was hydronephrotic.

Hydronephrosis was again noted on the right side on May 14, 1956; the left side remained normal. On November 16, 1956, the left side was still normal, but the superior calyx on the right side showed caliectasis. In 1957, the left side was still functioning normally, although hydronephrosis was seen on the right side in a film made on September 20. There were no stones in either kidney. The film dated April 28, 1958, showed the laminated calculus mentioned in the protocol, and I believe this was located in the kidney. There was no dye excretion on the right side or in the colon.

Two films showed a dilated small bowel with some loops. Although air in the colon was mentioned, we were not sure that it was present. Multiple fluid levels were demonstrated; they were rather widely separated and not dis-

FIGURE 3. Gross specimen of kidney and sigmoid colon showing ureteral anastomoses and infection and calculi in the left kidney.

FIGURE 4. Gross specimen showing adenocarcinoma on the cecal side of the ileocecal valve.

tinctive in any way. Use of the term "spastic ileus" is not correct in referring to this condition. This case had the appearance of an adynamic ileus rather than that of an obstruction.

To summarize these findings, I would like to point out that a series of intravenous pyelograms throughout the course of this patient's illness showed a poor-to-nonfunctioning right kidney, with a persistent hydronephrosis, and a normally functioning left kidney. Toward the terminal part of the illness, a laminated calculus was seen, which we believe to have been in the kidney. Two gastrointestinal series were made in 1952; however, the results of both were negative. A barium enema in 1953 also gave negative findings.

DR. VICTOR JABLOKOW (staff physician, laboratory service): The lesion which was removed from the cervix in this patient was reported as polypoid adenomyoma on April 13, 1950. The sections showed numerous benign endometrial glands with stoma in muscular tissue. This was a manifestation of the uterine adenomyosis which was found later after the uterus was removed. Dilatation and curettage on April 7, 1953, revealed numerous friable pieces of tissue. Histologically, there were many atypical glands, a loss of polarity, papillary projections, and anaplasia (figure 1). This represented papilliferous carcinoma of the endometrium. Subsequently, the uterus and adnexa were removed. There was evidence that the tumor had invaded the walls of the uterus.

A biopsy of the tumor removed from the bladder on March 15, 1956, showed transitional-cell carcinoma (figure 2). In some areas, the transitional character of the tumor could be recognized; in others, the tumor was very anaplastic. There were many mitotic figures, and the nuclei were irregular and hyperchromatic. Invasion of the wall of the bladder was

seen. Total cystectomy with implantation of the ureters into the rectosigmoid was done after this biopsy was performed.

Postmortem examination of this patient showed acute, generalized peritonitis. Approximately 1000 cc. of cloudy, foul-smelling fluid was present in the peritoneal cavity. The peritoneum was covered with fibrinopurulent exudate. A subdiaphragmatic and perirenal abscess was seen on the right side, with necrosis of the underlying psoas muscle. One stone, measuring 1 by 0.5 by 0.5 cm., was obstructing the left ureter at the midportion, with marked hydro-ureter and hydronephrosis above it (figure 3). A larger stone was present in the kidney pelvis. The lumens of the ureterosigmoidostomies were patent and showed no stenosis. The ileocecal junction revealed an adenocarcinoma which measured 2.5 by 1 by 1 cm. (figure 4). Histologically, it invaded the submucosa, but it had not metastasized. The right pleural cavity contained approximately 600 cc. of fluid and the left pleural cavity contained about 200 cc.; there was acute pleuritis over the right base. The uterus, adnexa and urinary bladder were surgically absent, and there were no metastases or recurrence of previously removed tumors.

This patient had endometrial carcinoma, transitional-cell carcinoma of the bladder, and adenocarcinoma of the cecum. Each of these tumors was a primary one. The patient died as a result of urinary sepsis from the ureterointestinal anastomoses.

MEETINGS and Postgraduate Courses

AMERICAN COLLEGE OF CARDIOLOGY, INDIANAPOLIS: Ninth annual convention, Claypool Hotel, May 23-28. For further information, write to: Dr. Philip Reichert, Executive Director, Empire State Building, New York 1.

BIOLOGICAL PHOTOGRAPHIC ASSOCIATION, SALT LAKE CITY: Thirtieth annual meeting, August 23-26, at the Utah Hotel Motor Lodge. For further information, write to: Howard E. Tribe, Division of Medical Illustration, University of Utah, Salt Lake City 12.

DUKE UNIVERSITY SCHOOL OF MEDICINE, DURHAM, NORTH CAROLINA: Medical seminar cruise to the Baltic Sea, June 5-28, sailing from Wilmington, North Carolina on June 5 or from New York on June 8. Shore excursions will include Le Havre, Cuxhaven, Leningrad, Helsinki, Stockholm, Copenhagen and Hamburg. For further information, write to: Dr. W. M. Nicholson, Assistant Dean in Charge of Postgraduate Education, Duke University School of Medicine, Durham.

FIFTH INTERNATIONAL CONGRESS ON NUTRITION, WASHINGTON, D. C.: To be held September 1-7 at the Sheraton Park and Shoreham hotels. For further information, write to: Sidney S. Negus, Medical College of Virginia, Richmond.

FIFTH INTERNATIONAL POLIOMYELITIS CONFERENCE, COPENHAGEN, DENMARK: To be held July 26-28 at the Falkonercentret. For further information, write to: Mr. Stanley E. Henwood, Executive Secretary, International Poliomyelitis Congress, 120 Broadway, New York 5.

INTERNATIONAL CONFERENCE ON CONGENITAL MALFORMATIONS, LONDON, ENGLAND: To be held July 18-22, under the sponsorship of the National Foundation. For further information, write to: Stanley E. Henwood, Executive Secretary, International Medical Congress, Ltd., 120 Broadway, New York 5.

INTER-SOCIETY CYTOLOGY COUNCIL, CHICAGO: Annual scientific meeting to be held at the Palmer House, September 23-25. For further information, write to: Dr. Paul A. Younge, Secretary, 1101 Beacon Street, Brookline 46, Mass.

THE NATIONAL FOUNDATION, NEW YORK: Fellowships for research in genetics and embryology are available for medical students who have completed at least one year of medical school. Applicants must be able to devote a minimum of eight consecutive weeks to full-time research. The stipend is $600. Each approved medical school may nominate one applicant in either field. Further details are available from medical school deans.

THIRD INTERNATIONAL CONGRESS OF PHYSICAL MEDICINE, WASHINGTON, D. C.: To be held August 21-26, 1960, at the Hotel Mayflower. For further information, write to: Executive Secretary, International Congress of Physical Medicine, 30 North Michigan Avenue, Chicago 2.

CLINICAL STUDY

Methoxypromazine Maleate in Cases of Psychoneurosis

TIBOR BODI, HOWARD LEVY, ISAIAH SHARE, JOHN H. NODINE AND JOHN H. MOYER*

Hahnemann Medical College and Hospital, Philadelphia

Methoxypromazine maleate apparently has the same sedative and tranquilizing action as chlorpromazine, but is less potent than the latter drug, particularly in cases of acute psychosis.

Clinical studies indicate that methoxypromazine maleate is suitable for the treatment of ambulatory patients with predominantly psychosomatic complaints. Studies so far indicate a minimal incidence of toxic or neurovegetative side effects.

TIBOR BODI

ALTHOUGH the phenothiazine derivatives are useful therapeutic agents, the incidence of serious side reactions, particularly agranulocytosis and liver damage, has caused considerable concern.[1-5] In addition, less serious side effects such as drowsiness, hypotension, parkinsonism, excessive gain of weight, menstrual disturbances and lactation have been observed in many cases in which these agents have been administered. In an effort to eliminate these toxic effects, a new compound, methoxypromazine maleate (TENTONE® maleate), was prepared by substituting a methoxy group for the chlorine in chlorpromazine[6] (figure 1).

Animal experiments have not revealed that this compound has any toxic effect on the liver or blood. Its tranquilizing effect was found to approximate that of chlorpromazine, but it did not disturb the menstrual cycle of adult virgin rats. Its use in cases of psychosis likewise did not cause any toxic effect on the

*Departments of Medicine and Psychiatry, the Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania.

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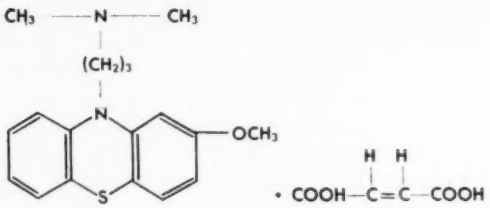

FIGURE 1. Methoxypromazine maleate.

liver or blood. Consequently, an investigation of this compound was undertaken in clinical cases in which the patients were ambulatory and had to keep up their regular activities. The primary purposes of this study were to determine the useful dose, to evaluate the short-term results of the treatment of selected psychosomatic problems, and to determine what side effects might be expected to occur in cases in which this compound is used.

Material and Method of Study

Thirty-seven cases were selected from the general medical clinic of the Hahnemann Hospital after complete medical examination had been made and after routine laboratory tests had been performed. These cases were selected because the primary problem was believed to be psychosomatic. Table 1 shows the diagnosis that was made in these cases. The age of the patients ranged from 14 to 76 years. Twenty-three of the 37 patients were Negroes; 29 of the patients were females and eight were males.

Treatment was started by administering 10 to 50 mg. of methoxypromazine maleate three times a day. If side effects became troublesome, the dose was decreased. On the other hand, if clinical improvement was incomplete, the dose was increased. After the optimal dose had been determined, it was administered three times a day for four to six weeks. Various doses of the drug were administered for a total of 1,760 days. A dose of 10 mg. was administered three times a day for an average period of 26 days in 14 cases; a dose of 25 mg. was administered three times a day for an average period of 37 days in 25 cases, and a dose of 50 mg. was administered three times a day for an average period of 32 days in 15 cases. In 19 of the 37 cases, a placebo was administered after the administration of the methoxypromazine maleate was discontinued.

A special team consisting of internists, a psychiatrist and a social worker observed the patients at weekly or biweekly intervals during the course of the study. Evaluation of the results was based on subjective reports as well as on objective observation of the patients at consecutive interviews. In order that the patients would not be influenced by suggestion in reporting their condition, stereotyped questions were not used and psychotherapy was intentionally avoided except for the casual reassurance necessary to obtain the patients' cooperation. If improvement was questionable, the result was classified as no improvement; if the drug produced little more than partial relief of the symptoms, the result was classified as slight improvement; if the drug produced highly significant relief of the symptoms, the result was classified as moderate improvement; if only minimal symptoms remained at the completion of treatment, the result was classified as marked improvement. The designation complete relief of symptoms is self-explanatory.

Results

Definite improvement (slight improvement, moderate improvement, marked improvement or complete relief of symptoms) occurred in 30 (81 per cent) of the 37 cases in which methoxypromazine maleate was administered, and highly significant improvement (moderate improvement, marked improvement or complete relief of symptoms) occurred in 24 (65 per cent) of the 37 cases (table 2). These results are in marked contrast to the results in the 19 cases in which a placebo was administered alone. Definite improvement occurred in only seven (37 per cent) of these 19 cases, and highly significant improvement occurred in only six (32 per cent) of the cases (table 3). The smallest dose of methoxypromazine maleate that produced complete relief of symptoms or produced the maximal degree of slight, moderate or marked improvement was as follows: a dose of 25 mg. admin-

TABLE 1

CLINICAL DATA IN 37 CASES OF PSYCHONEUROSIS

CASE	AGE (Years)	SEX	RACE	DIAGNOSIS
1	39	F	Negro	Anxiety reaction associated with latent syphilis
2	48	F	Negro	Anxiety reaction associated with hypertension
3	60	M	White	Anxiety reaction associated with bronchial asthma
4	52	M	Negro	Anxiety reaction associated with alcoholism
5	42	F	White	Anxiety reaction
6	54	F	White	Anxiety reaction associated with ulcers and Paget's disease of nipple
7	50	F	White	Anxiety reaction with hysterical features
8	34	M	White	Anxiety reaction associated with ulcer
9	35	F	Negro	Anxiety reaction associated with rheumatic fever and compensation neurosis
10	54	F	White	Anxiety reaction
11	21	F	Negro	Anxiety reaction
12	27	M	Negro	Anxiety reaction after pneumonectomy for pulmonary tuberculosis
13	35	F	White	Anxiety reaction
14	48	F	Negro	Anxiety reaction and menopausal syndrome
15	68	F	White	Anxiety reaction and gallbladder disease
16	23	M	White	Anxiety reaction
17	30	F	White	Conversion reaction
18	43	F	Negro	Hysteria associated with anxiety and phobia
19	24	F	Negro	Conversion reaction
20	47	F	Negro	Conversion reaction associated with hypochondriasis and obsessive personality
21	74	F	White	Reactive depression associated with somatization
22	27	F	Negro	Conversion reaction
23	23	F	White	Conversion reaction
24	14	F	Negro	Conversion reaction
25	43	F	Negro	Conversion hysteria
26	76	F	White	Adjustment reaction of late life
27	42	F	Negro	Conversion hysteria
28	40	F	Negro	Conversion reaction
29	58	M	White	Paranoid personality
30	15	M	Negro	Adolescent reaction
31	59	F	Negro	Hypochondriasis
32	30	F	Negro	Hysterical personality associated with uterine bleeding
33	21	F	Negro	Psychophysiologic reaction
34	46	F	Negro	Psychophysiologic reaction associated with obesity
35	48	F	Negro	Psychophysiologic gastrointestinal reaction
36	32	F	Negro	Schizophrenic reaction
37	56	M	Negro	Paranoid reaction

istered three times a day in 18 cases, a dose of 10 mg. administered three times a day in six cases, and a dose of 50 mg. administered three times a day in six cases.

A serious toxic reaction was not observed in any of the cases in which methoxypromazine maleate was administered. Transitory and minimal sleepiness occurred in three cases in which 25 mg. of the drug was being administered three times a day and in two cases in which 50 mg. of the drug was being administered three times a day, but this did not necessitate any change in the dose. Significant drowsiness occurred in three other cases in which 25 mg. of the drug was being administered and in one case in which 50 mg. of the drug was being administered three times a day, but the drowsiness responded readily to a reduction in the dose. In one case, minimal pain in the breast occurred while the drug was being administered, but examination did not reveal any evidence of congestion or lacta-

TABLE 2

RESULTS OF ADMINISTRATION OF METHOXYPROMAZINE MALEATE

DIAGNOSIS	CASES	RESULTS				
		Complete relief of symptoms	*Marked improvement*	*Moderate improvement*	*Slight improvement*	*No improvement*
Anxiety reaction	16	2	4	3	4	3
Psychoneurosis (other than anxiety)	12	1	7	1	1	2
Personality disorders	4		1	1	1	1
Psychophysiologic reaction	3		1	2		
Schizophrenic reaction	1		1			
Paranoid reaction	1					1
TOTAL	37	3	14	7	6	7

TABLE 3

RESULTS OF ADMINISTRATION OF A PLACEBO

DIAGNOSIS	CASES	RESULTS				
		Complete relief of symptoms	*Marked improvement*	*Moderate improvement*	*Slight improvement*	*No improvement*
Anxiety reaction	6		1		1	4
Psychoneurosis (other than anxiety)	10	1		3		6
Psychophysiologic reaction	3			1		2
TOTAL	19	1	1	4	1	12

tion. The patient in this case was a 24 year old Negro woman. Since this patient had conversion hysteria, the subjective nature of the pain occurring in the breast must be taken into consideration.

The occurrence of menstrual disturbances or a significant gain in weight was not reported by any of the patients, but one patient with advanced cirrhosis reported a definite increase in appetite. Laboratory procedures including a total leukocyte count, a differential leukocyte count, a thymol turbidity test, a cephalin-cholesterol flocculation test and urinalysis were used, but they did not disclose any abnormality during or after administration of the methoxypromazine maleate. The drug did not have any hypotensive effect. There was no suggestion of syncope or disturbance of balance during the course of treatment. In one case in which hypertension had been present before treatment was started, the blood pressure remained normal during the treatment.

Case Reports

Case 17 (table 1)—A 30 year old Puerto Rican married woman complained of multiple symptoms, including nightmares, backache and infrequent epigastric distress, which were precipitated by her husband's desertion. Owing to the responsibility of four small children, financial problems, language difficulties, and continued beatings by her husband even after their separation, she had suicidal im-

ulses and even had an urge to kill the baby n her arms. She felt that the ground was inking under her. She realized, however, that he would not kill her infant. Her father, like her husband, had been an alcoholic, and he frequently had beaten both her and her mother.

Thorough medical examination did not reveal any organic cause for her somatic symptoms. She was referred to the psychiatric clinic, and her children were temporarily placed in a home. The psychiatric consultant believed that the patient had a conversion reaction, but he did not believe that she was psychotic.

Methoxypromazine maleate was administered in doses of 50 mg. three times a day. She immediately felt less nervous and no longer had a suicidal or homocidal urge. Administration of a salicylate caused the backache to disappear. After the administration of methoxypromazine maleate had been continued for eight weeks, her mood improved and she was asymptomatic except for her customary mild and infrequent epigastric distress. Her backache did not recur after the administration of the salicylate was discontinued. Her children were returned to her, and she was extremely grateful for the help that she had received.

Case 21 (table 1)—A single woman, aged 74 years, had always been well and had worked as a domestic until the death of her employer. She subsequently had become very lonely and withdrawn. Severe crampy pain had developed in the middle of the abdomen. The pain had not been related to the ingestion of food, but it had been associated with severe habitual constipation. The patient had been admitted to the hospital on several occasions. On these occasions, complete roentgenologic examination of the gastrointestinal tract had not disclosed any pathologic lesion.

The consulting psychiatrist believed that the patient had a reactive depression associated with somatization. Methoxypromazine maleate was administered in doses of 25 mg. three times a day. Moderate to marked improvement occurred during the next six weeks. Administration of 50 mg. of the drug three times a day did not produce any further improvement; in fact, some of the abdominal symptoms, especially the constipation, recurred. Administration of laxatives controlled these recurrent symptoms.

When a placebo was substituted for the methoxypromazine maleate, the patient again complained of cramps and severe constipation. When the administration of the 50 mg. dose of methoxypromazine maleate was resumed, it alleviated most of the symptoms.

In this case, the administration of methoxypromazine maleate and the correction of longstanding constipation controlled the depression. In spite of the patient's advanced age, she tolerated the administration of 50 mg. of methoxypromazine maleate three times a day. Leukocyte counts, determinations of the profile of the liver, and urinalyses were made repeatedly, but they did not reveal any evidence of toxic side effects.

Case 27 (table 1)—A 42 year old Negro woman was observed in the medical clinic after she had had an episode of "shortness of breath," a "tired feeling" in the chest, and "fluttering" of the heart. This episode had occurred while she had been cooking, but she previously had had similar episodes that had not been related to exertion.

The most recent episode had been precipitated by a visit by the patient's sister. The patient had become extremely angry at her sister's domineering and inconsiderate attitude. The patient was excessively religious, apparently in an effort to protect herself from her hostile impulses. She did not have any good heterosexual relationships, for which she blamed herself.

Complete physical examination, including electrocardiographic examination by a cardiac consultant, did not reveal any organic disease. Psychiatric consultation confirmed the diagnosis of conversion hysteria.

Methoxypromazine maleate was administered three times a day in doses of 25 mg. The "tired feeling" in the chest subsided. The patient reported that she was greatly improved and that she was better able to rest. She appeared definitely more calm and perhaps slightly indifferent. After the administration of this dose of the drug had been continued

for one month, the patient no longer feared that she had a serious cardiac disease, and she tolerated the death of a friend quite well. One month later, the dose was increased to 50 mg. The patient continued to improve except for the occurrence of one mild hysterical attack of a "pulling" sensation in the chest. After the administration of this dose had been continued for six weeks, a placebo was substituted for the methoxypromazine maleate. Headaches and nervousness recurred a short time later, but the patient did not become as seriously disturbed as she had been before the administration of methoxypromazine maleate was started.

No change was observed in the blood pressure, pulse rate, blood count or concentration of serum transaminase during the time that the methoxypromazine maleate was administered, and the thymol turbidity test and the cephalin-cholesterol flocculation test did not show any evidence of a toxic reaction. However, the patient did complain of a transient sleepy feeling, but this subsided without any change in the dose of the drug. The result of treatment in this case was classified as marked improvement.

Comment

Pharmacologic investigation has revealed that the action of methoxypromazine maleate on the autonomic and central nervous systems is similar to that of chlorpromazine.[7] Clinical use of this drug by French investigators has indicated that it has the same sedative and tranquilizing action as chlorpromazine.[6] However, it is less potent than chlorpromazine, particularly in cases of acute psychosis. The French investigators also have noted that such neurovegetative side effects as orthostatic hypotension, tachycardia and extrapyramidal manifestations either are mild or do not occur in cases in which this drug is used. These characteristics make the drug eminently suitable for the treatment of ambulatory patients.

The disproportionately great number of cases of anxiety and other types of psychoneurosis observed in the medical outpatient clinic has created a demand for therapeutic agents capable of producing sedation without the danger of addiction or interference with normal mental acuity. In most of the cases used in our study, the patients previously had been treated with barbiturates, chloral hydrate, meprobamate, placebos and simple psychotherapy, but this treatment had proved ineffective. Phenobarbital, which is frequently used in the treatment of psychoneurosis, is not the ideal drug, because it induces sleepiness and dulls intellectual performance.[8] In addition, the administration of large doses of this drug may result in addiction.

Anxiety was the most common type of neurosis in the cases used in our study. The variability of response in cases of this type of neurosis made evaluation of the results of treatment difficult, but careful observation and the avoidance of formal psychotherapy reduced this variable.

It has been our experience that the action of methoxypromazine maleate is very similar to that reported by French investigators. It was moderately effective in most of our cases of anxiety neurosis, and it was definitely better than a placebo. In cases in which it produced improvement, it relieved the anxiety and enabled the patients to relax. The patients generally requested more of the drug. In cases in which the patients responded well to the use of the drug, low doses were effective. A slight hypnotic action occurred in a few cases, but this was eliminated by reducing the dose. No significant toxic reaction occurred, and laboratory tests did not reveal any evidence of hematologic, renal or hepatic damage.

We believe that methoxypromazine maleate is useful in the treatment of acute anxiety. Although it apparently is less potent than chlorpromazine, it seems to be more suitable for the treatment of ambulatory patients because of its low hypnotic potential.

No attempt was made to evaluate the antiemetic effect of this drug, but previous experiments on dogs would suggest that it does have an antiemetic action.[9]

If further study supports the finding that this drug does not cause neurovegetative or other toxic effects, it may prove better suited than other phenothiazine derivatives for the treatment of ambulatory patients.

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Books Received

Books received are acknowledged, and, as space permits, those of principal interest to our readers are reviewed more extensively. Reviews appear in this issue starting on page A-170; additional listings are on pages 454, 479 and A-182.

Pediatric Dermatology. By Henry H. Perlman, M.D., Clinical Professor of Pediatrics, Jefferson Medical College of Philadelphia. 477 pages with 203 illustrations. 1960, The Year Book Publishers, Inc., Chicago. $18.00.

Emotional Forces in the Family. Edited by Samuel Liebman, M.D., Clinical Assistant Professor of Psychiatry, University of Illinois College of Medicine, Chicago, with nine contributors. 157 pages. 1959, J. B. Lippincott Company, Philadelphia. $5.00.

Roentgen Examinations in Acute Abdominal Diseases. By J. Frimann-Dahl, M.D., Professor of Roentgenology, University of Oslo, Norway. Ed. 2. 518 pages with 446 illustrations. 1960, Charles C Thomas, Springfield, Illinois. $15.50.

Back Pain; Diagnosis and Treatment Using Manipulative Techniques. By John McM. Mennell, M.D., Special Lecturer, Department of Physical Medicine, College of Medical Evangelists, Loma Linda-Los Angeles. 226 pages with 78 illustrations. 1960, Little, Brown & Company, Boston and Toronto. $9.50.

Antithrombotic Therapy. Modern Medical Monographs. By Paul W. Boyles, M.D., Instructor in Medicine, University of Miami School of Medicine, Coral Gables. No. 20. 131 pages, illustrated. 1959, Grune & Stratton, Inc., New York and London. $3.00.

Chemical Micromethods in Clinical Medicine. American Lecture Series. By R. H. Wilkinson, M.D., Assistant Chemical Pathologist, The Hospital for Sick Children, London, England. 121 pages with 18 illustrations. 1960, Charles C Thomas, Springfield, Illinois. $5.00.

Diagnosis and Treatment of Tumors of the Chest. Sponsored by the American College of Chest Physicians. Edited by David M. Spain, M.D., Associate Professor of Pathology, Columbia University College of Physicians and Surgeons, New York, with 26 contributors. 371 pages, illustrated. 1960, Grune & Stratton, Inc., New York and London. $14.75.

Some Papers on the Cerebral Cortex. American Lecture Series. Translated by Gerhardt von Bonin, Professor of Anatomy, University of Illinois College of Medicine, Chicago. 396 pages with 42 illustrations. 1960, Charles C Thomas, Springfield, Illinois. $11.50.

Functional Anatomy of the Limbs and Back. A textbook for students of physical therapy and others interested in the locomotor apparatus. By W. Henry Hollinshead, Ph.D., Head, Section of Anatomy, Mayo Clinic, Rochester, Minnesota. Ed. 2. 403 pages with 159 illustrations. 1960, W. B. Saunders Company, Philadelphia and London. $9.00.

The Year Book of Obstetrics and Gynecology (1959-1960). Edited by J. P. Greenhill, M.D., Professor of Gynecology, Cook County Graduate School of Medicine, Chicago. 573 pages with 27 illustrations. 1959, The Year Book Publishers, Inc., Chicago. $8.00.

Surgical Philosophy in Mass Casualty Management. By Warner F. Bowers, M.D., Colonel, and Carl W. Hughes, M.D., Lieutenant Colonel, Medical Corps, Tripler U. S. Army Hospital, Honolulu. 204 pages. 1960, Charles C Thomas, Springfield, Illinois. $6.75.

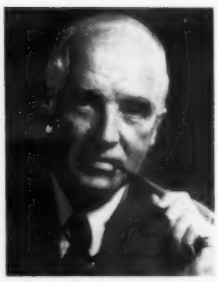
Leukocyte Antigens and Antibodies. By Roy L. Walford, M.D., Assistant Professor of Pathology, University of California at Los Angeles School of Medicine. 182 pages. 1960, Grune & Stratton, Inc., New York and London. $6.75.

Current Therapy 1960. Edited by Howard F. Conn, M.D., with 12 consulting editors. 808 pages. 1960, W. B. Saunders Company, Philadelphia and London. $12.00.

Unfinished Researches

CHARLES H. BEST*

University of Toronto Faculty of Medicine, Toronto



CHARLES H. BEST

EVERYONE who completes a successful research project has the wonderful experience of seeing unexplored country. The peaks which he can see may be higher or lower than the one he has climbed. The explorer knows that there will be a rush toward the most spectacular new areas as soon as he describes his route and his vistas. He would rather like to reserve a few special places for his own further exploration but this is seldom possible, and if a great many people choose to extend and develop his findings, as they will if his report suggests the existence of new treasure, he has little chance of remaining in the van unless he organizes a fast-moving team and drives hard. Sometimes, however, he has been attracted by a particular new formation which does not appeal to other adventurers and he can return, almost at his leisure, to develop this mine of information. It may prove to be a rich one and may lead our explorer by a direct route to an advanced position on the main vein of progress in his field. Some research workers are by nature and temperament explorers, others are developers. Both types of workers are, of course, necessary if we are to move forward and to consolidate our advances.

The waves of contemporary research wash away all but the most prominent and durable landmarks of previous accomplishment. Small advances are rediscovered in stride, as it were, and little or no credit is given to the one who first saw the light or who first convinced the world that it was there. I have a vivid recollection of my own outlook nearly 40 years ago and I do not suppose that it differed essentially from that of the youthful research worker of today. I know that we failed to gain a few friends because we inadvertently omitted mention of some minor contributions to our subject. In one case we seem to have made a downright enemy by overlooking papers which contributed extremely little.

*Professor and Head of the Department of Physiology, University of Toronto Faculty of Medicine, and Director of the Banting and Best Department of Medical Research, Toronto, Ontario, Canada.

This address was presented at the Centennial Celebration, September 29, 1959, of Northwestern University Medical School, Chicago, Illinois, and is reprinted with permission from the *Quarterly Bulletin* of Northwestern University Medical School.

My personal experience in research must resemble closely those of others in different fields. Most of the peaks which we could see from insulin have been scaled, but there are some which have resisted all efforts and a few, perhaps more than we realize, which have not really been attempted. To keep my remarks in line with my title I should refer only to those researches which have not been finished.

The mechanism of the action of insulin is a rugged one with which to start. The first experiment, even before we had amassed all the data which proved that a potent antidiabetic substance could always (i.e., in 75 consecutive experiments without a failure) be extracted from the pancreas, was to add a potent extract to shed blood and determine the effect on the rate of disappearance of sugar under standard conditions. The findings were negative; i.e., no effect could be detected but with refined methods, using concentrated preparations of certain stages of the formed elements of the blood, definite progress which I will not attempt to review has now been made by other workers. This research may, however, be said to be unfinished. The fate of the sugar which leaves the blood under the influence of insulin is now fairly well settled. After a team of workers had been formed, Fred Banting chose as his personal problem—as it were—the study of the effect of insulin on liver glycogen in completely depancreatized dogs. The effect was dramatically positive, but one can ask many searching detailed questions in this field without finding all the answers available.

My own choice in 1921 was the effect of insulin on the burning of sugar. The respiratory quotient was our only index in depancreatized dogs in those days. It strongly indicated an increased combustion of sugar after insulin. We all appreciate how indefinite such findings are in the light of recent knowledge but I can think of a lot of experiments with C^{14} dextrose which would reveal information on the time relationship of the acceleration of combustion of sugar by insulin which have not been performed.

We gave insulin orally and rectally in 1921 and could find no evidence of absorption. Some authorities think that it will be impossible to make a form of insulin which will be active when given by mouth. I do not share this view and look upon the problem of the enteral administration of insulin as an unfinished research.

The most physiologic way of giving insulin is by continuous intravenous injection. I remember making this remark in Toronto about 37 years ago. Little success has attended the weak and abortive efforts to prepare a compound from which insulin is released at a rate in proportion to the concentration of sugar or of some other substance indicative of the diabetic state. The direct attack on this problem may be unproductive but we must think of some indirect approach. The research is unfinished.

One could easily give several full lectures on researches relating to insulin which have not been completed, but I will give only one further example before turning to other subjects. In the early 1920s a relationship between insulin administration and ADRENALIN® liberation was established. This was the forerunner of many interrelationships between the antidiabetic and other hormones. Isolated facts are interesting but what we must know precisely in quantitative terms is the whole series of endocrine changes which result from lessening or raising the rate of liberation of one member of the group. We are far from this happy state.

I worked for some years on histamine and choline and with Dale, Dudley and Thorpe, we isolated the former from bacteriologically uncontaminated tissue for the first time. I was keenly interested for several years in an enzyme system which I named histaminase but this field has grown out of all recognition. The availability of labeled histamine has permitted the demonstration of half a dozen histaminases, and youthful investigators are even threatening to throw away the term which I introduced. The histamine liberators and the antihistamines have added tremendously to the importance and interest of this broad area, and I have not allocated enough of my reading time to it to permit me to discuss it intelligently. But I did have an early glimpse which stimulated the formation in my mind

of a lot of problems, some of which are still unsolved. I would like to know much more about the exact locus and the time relationships of the actions of all the physiologic vasodilators.

During the 1930s my colleagues and I worked hard on the purification of heparin and the establishment of its role in the prevention of many types of experimental thrombosis. Just before the second world war completely changed the direction of our research effort, we had established that heparin could prevent a type of coronary thrombosis which we could produce at will in dogs. The ramifications of this research seemed endless at that time and, while we have witnessed the clinical application of our findings and the extension of the experimental aspects of this work, there are scores of problems awaiting solution which were as obvious 25 years ago as they are today. The mechanism by which heparin prevents thrombosis is still unknown. There has been no vigorous and comprehensive attempt to detect the human patient in whom thrombosis is likely to occur. There is plenty of room for better long-acting heparins and the need for this has not been completely filled by the DICUMAROL® derivatives. Progress is being made very rapidly but there are many unfinished researches.

My first interest in choline was in its vasodilating action, and I learned how to isolate it from tissues, to acetylate it, and to assay the acetylcholine, when I was working with Dale and Dudley in London in 1928. A few years later, with Huntsman and Hershey, we identified choline as the main component of crude egg yolk lecithin which Hershey and Soskin had found to exert the same dietary protective effect on the liver as did something contained in or made available by fresh beef pancreas. I will not even outline the present position of what I have called the lipotropic effect of choline, protein, etc. Choline is well established as one of the B vitamins and methionine is its main dietary precursor. The titles of the unfinished researches in the choline field could fill a volume. When we first saw the dramatic effects of lack of choline in animals we expected that somewhere in the world someone could justify changing the multiple deficiencies of a few individuals among the many millions into a specific deficiency of choline and methionine. This has never been done thoroughly, and we do not know the effects of inadequate dietary amounts of the lipotropic factors in man. It would be vastly stimulating to the experimentalist to know this, and I believe that valuable knowledge could be gained without endangering a single human life.

I am giving a special lecture on glucagon at these meetings but I may be permitted to point out here also a few unfinished researches. What is the physiologic role of this peptide produced in the alpha cells of the pancreas? Why should it have some of the same actions as steroids from the adrenal cortex and as Adrenalin from the adrenal medulla? Will we discover some specific action of glucagon? Will we find clinically clear-cut cases of hypo- and hyperglucagonemia?

I have recently been asked to prepare a lecture entitled "Forty years of insulin research." I could also give one on "Thirty years of choline research," or "Thirty years of heparin research." I have been interested in fat transport for 40 years and feel that insulin, choline, the fat-mobilizing substances of the anterior pituitary, and purified heparin have contributed to our knowledge of this subject. In fact I think that certain of them are vital physiologic factors in this field. I have, however, read recent very fine reviews on fat transport, in which none of these old friends were adequately presented and some were not mentioned. The reviews were at the so-called cellular level, and I would agree that we must know all we can about the general physiologic factors which control the formation and breakdown of all the fat moieties within cells and their transport between cells, but we probably should not hesitate to call in the hormones, vitamins and humors since processes which occur in the absence of these factors may be quite unphysiologic. I will not develop this subject since we all know that isolated mammalian cells lacking all sorts of homeostatic mechanisms may give peculiar answers to our questions.

I have recently received word from a friend of very long standing, Professor A. V. Hill, F.R.S., that some work in which Professor D. Y. Solandt and I were concerned during the war had been of considerable value to the United States Navy. The idea of using a certain wavelength of red to illuminate airplane cockpits and charts and instruments on the bridges of ships originated with the late Dr. Lythgoe of University College, London. Preliminary tests at sea just before the war started were not successful. Red lighting preserves night vision which is vitally important for operations in the air or at sea, or for that matter on the land, when the illumination is very low. That is when the rods, not the cones, of the eyes are used. Professor Hill suggested to us in 1940 that we reinvestigate this problem. In the laboratory we found dramatically favorable results and then moved to Halifax where we used naval officers as our experimental subjects. They were extremely enthusiastic and we installed, for the first time, red lighting in naval vessels. Professor Walter Miles heard our description of this work and moved rapidly to confirm and extend it, and soon most U. S. naval vessels had red lighting. Installation proceeded at a somewhat slower rate in the Royal Navy and Royal Canadian Navy. Professor Lythgoe's idea and Professor Hill's dissemination of it bore fruit. It is not difficult to think of further extensions of this work which have not to my knowledge been made.

The measure of success which was granted me at the beginning of my career may account in part for the fact that I have always been, and continue to be, most optimistic in attacking research problems. I suppose that most workers who persist in their investigations are *ipso facto* optimists. We physiologists and biochemists feel that substances found in tissues must serve some interesting purpose. We feel that "man's inability to comprehend" is our limiting factor and not "Nature's unwillingness to reveal." We are willing to invest our efforts in the study of any interesting phenomenon for which our minds can formulate a possible mechanism, and if our minds fail us in this regard we carry on anyway, exploring and eliminating unessential material until our main problem becomes simpler and clearer. Our work is, of course, never finished.

Editorials

Postgraduate Medicine

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CHARLES W. MAYO, M.D.

Contributing Editor:
MORRIS FISHBEIN, M.D.

Executive Editor:
SYLVIA COVET

REACTION OF INTERNS TO INTERNSHIPS

UNDER the auspices of the Association of American Medical Colleges, a division of research, headed by Helen Hofer Gee, has completed many studies which will aid in planning certain aspects of medical education for the future. One study was concerned with the characteristics of interns and internships in the period 1958 to 1959. Interns felt that the internship was a valuable experience above and beyond the clerkship. About 1 in 20 interns felt that the internship had been of little or no value. Although the vast majority of medical college graduates believed that the internship made some contribution to their development, a considerable proportion found the experience to be simply a duplication of effort. The internship is believed to be a continuation of the educational process; nevertheless, about half of all rotating and surgical interns felt that their work was inadequately reviewed. Indeed, many interns seemed to feel that they were simply rendering a service in getting some practical training without much extension of their education.

As a result of these studies, Drs. Gee and Schumacher conclude that the internship serves as something of a breather for the individual who is going on to residency training. "The intern who faces imminently the responsibilities of a career in general practice, however,—and who is not particularly well endowed intellectually, whose medical school struggled with problems of inadequate finances. and who is serving a rotating internship in a nonteaching hospital—is far less complacent, and evidently with reason."

They conclude finally, "The data in this study tend to support the popular view of the internship as a period of indentured servitude for many young physicians. Where such conditions exist, one is forced to inquire as to the inadequacy of mechanisms for approving internships and to inquire as well into the ethics of demands for service in the guise of fulfilling an educational requirement made by the medical profession."

Another chapter in their preliminary report deals with the factors affecting the choice of an internship and an analysis of the data ac-

cumulated in 1958 on the internship. This leads to the conclusion that the curriculum might be revised so that the internship will be included with the undergraduate program. The final chapter is on the physician-patient relationship. Here it is concluded that in the past formal teaching played an insignificant role in developing skill in physician-patient relations. Those who received their M.D. degrees in 1950 learned by observation during medical school and by trial and error after graduation.

It would seem that there are still many unsolved problems in medical education, and the investigators encourage much more experimentation with a view to finding better solutions for some of these problems. The final report is to be published in October 1960.

MORRIS FISHBEIN

THE STORY OF A NEW DRUG

In 1959 the pharmaceutical industries spent, according to Mr. John T. Connor,[1] president of Merck & Co., Inc., almost $200 million in research. The expenditure of Merck & Co. itself increased 75 per cent in five years, to a total of $17 million annually. Mr. Connor points out that the company spends more on research than has been paid to stockholders in dividends—and the stockholders are pleased with the results. Out of this type of expenditure came the product chlorothiazide, sold under a variety of trade names, which in itself is one of the great medical contributions of recent years.

In 1943 a basic research project called the Renal Program was launched. Over the following 16 years this program, which combines basic research and drug development, produced two major results. So much was learned about the physiology of the kidney that much in the textbooks needed to be rewritten. Moreover, two successful new drugs were found, although many more were discarded as failures. One of the first projects was to find a drug that would inhibit the elimination of penicillin through the kidney. The first drug produced required such a large dose to be effective that it was considered a failure. After three more years carinamide was found; however, it was also a failure, even though the inhibitor dose was diminished to 20 gm. a day. In the process of this investigation evidence showed that the kidney could filter, could secrete through the tubules, and could reverse this action and reabsorb into the blood. In 1951 BENEMID® was developed for blocking penicillin excretion; however, by this time it had become unnecessary, because penicillin could be made so abundantly and cheaply that inhibition of its excretion was hardly necessary. Nevertheless, Benemid was found to be useful in gout by maintaining lower uric acid levels, and this was a reward quite sufficient for the expenditure that had been made over eight years in what seemed to be unproductive research.

At the Peter Bent Brigham Hospital, Dr. William B. Schwartz had announced that sulfanilamide showed promising diuretic properties but was too toxic to be used for that purpose. The same group that produced Benemid undertook a search for a drug that would enhance the excretion of sodium chloride; they produced one called DIRNATE®, which was considered an orally effective diuretic. However, Dirnate was soon found to be ineffective, since it was not absorbed into the blood when administered in tablet form. The work assumed greater intensity when DIAMOX® (acetazoleamide) was discovered. From the intensified research came eventually the synthesis of the first compound of the chlorothiazide class. The drug was called DIURIL®. Extensive studies were made first on animals and later on human beings to determine toxicity, elimination by the body, and similar facts.

One year after the synthesis of chlorothiazide, the first tests on man were started. The product was described to seven physiologists specializing on the kidney, two of them from the National Heart Institute. Clinical testing continued for 14 months. By June 1957 the product had been distributed to 250 selected clinicians in the United States and 54 in 18 foreign countries. It was first tried by physicians in teaching hospitals in many specialties. By the time the product was made available generally to the medical profession after

its release by the Food and Drug Administration, over 1000 physicians had tested it on patients. The demand was immediately so great that a new plant was built at a cost of more than $1.5 million. More recently, as a result of continued research, HYDRODIURIL®, a more potent chlorothiazide analog, was released.

Mr. Connor, in his address to the American Association of Medical Clinics, noted that the product was patented and that its use for diuresis in over one million patients annually and in 500,000 patients with hypertension more than justifies the research outlay on the product. Meanwhile, Ciba Pharmaceutical Products, Inc. developed hydrochlorothiazide and the laboratories of Squibb, Schering, Bristol-Myers and Pfizer announced related compounds.

Mr. Connor ended his address with a challenge to communism to do a better job than American capitalism has done in discovering, developing, producing and distributing new and effective drugs. In the 42 years since the Russian Revolution, not one major drug discovery has been announced from the communistic countries. Mr. Connor said that at best they developed such products as could be made by pirating the results of American research, but even the production of such imitations is miserably slow.

The story of chlorothiazide may well stand beside other great contributions to chemotherapy such as the arsphenamines, sulfonamides and similar preparations. Mr. Connor does well to tell this story so that the American people may be aware of the significance of pharmaceutical research for the lengthening of life and the lessening of disease.

MORRIS FISHBEIN

REFERENCE

1. CONNOR, J. T.: The search for new weapons of life. Group Practice, November 1959.

"GUT"

ANNOUNCEMENT comes that the gastroenterologists of Great Britain will soon have a new periodical representing their interests. The name of the publication will be *Gut*. Just why they hesitated to call it the *British Journal of Gastroenterology* or some similar title and chose rather a word which means one thing in England and another in the United States is difficult to conjecture. The "Oxford Dictionary" describes "gut" as meaning on collective plural "the contents of the abdominal cavity; the bowels, entrails," and then says, "formerly in dignified use with regard to man." Since 1893 the word has been used in slang as signifying spirit or force of character. Under medical definitions, the "Oxford Dictionary" makes "guts" synonymous with intestine but says, "since 1460 the whole of the alimentary canal or its lower portion," and, in singular, "the belly or stomach, especially as the seat of appetite or gluttony," and then says, "now dialect and vulgar."

"Webster's New International Dictionary," unabridged, says that the plural means "bowels or entrails" but adds in italic *"now coarse."* Here also the plural signifies "the belly, the stomach, and hence gluttony" and as an alternate "stamina, courage or force."

In a discussion with an eminent gastroenterologist and a surgeon, the conclusion was reached that the British would do much better in this instance to follow the German pattern, which would probably give as a suitable title for such a publication *Allgemeine Zeitschrift für Darm und Verdauungskrankheiten.*

MORRIS FISHBEIN

THE MAKING OF A LIBRARY

ON the sixtieth birthday of Dr. John F. Fulton, November 1, 1959, his friends presented to him a book composed of the letters of Harvey Cushing, Arnold C. Klebs and John F. Fulton related to the establishment of the Historical Library at Yale.[1] The letters represent the conception of the brilliant idea to begin a medical-historical library at Yale University with the volumes accumulated by Harvey Cushing, Arnold Klebs and John Fulton. Fulton has been the catalyst for the developments around Yale University related to medical history which now make it one of the great medical-historical centers of the world.

On February 12, 1940, Arnold Klebs wrote

to George Stewart, his son-in-law, the definitive letter which tells the story *in toto*. He had thought of a historical institute long before, and for 25 years had been collecting toward such a library. On March 21, 1940, the name was definitely determined as the Yale Medical Library, and on April 4, 1941, the historical library was opened. Dr. Klebs died in 1943, and his books were added to those of Cushing and Fulton in 1946. Since that time other accumulations dealing with weights and measures, anatomy, marine biology, medical caricatures and surgery have been added.

A department of the history of medicine was established in February 1951, at which time John Fulton resigned his professorship of physiology to become its chairman and Sterling Professor of the History of Medicine.

It is well that the history of this event should be recorded in the original documents now made available.

MORRIS FISHBEIN

REFERENCE

1. The Making of a Library: Extracts From Letters 1934-1941 of Harvey Cushing, Arnold C. Klebs, and John F. Fulton. New Haven, Yale University, 1959.

"JOURNAL OF LIPID RESEARCH"

VOLUME 1, number 1 of the *Journal of Lipid Research* appeared in October 1959. Most unusual among medical publications is this highly technical journal, which is devoted almost wholly to original work in the chemistry, biochemistry, enzymology, histochemistry and physiology of the lipids. Workers in this field are so concerned with the technology of their study that they feel the need for a special publication devoted almost entirely to this aspect of their work.

To publish this new journal, a nonprofit organization was formed called Lipid Research, Inc. A grant was obtained from the National Heart Institute, and the technic of publishing was given over to University Publishers, Incorporated, New York, another nonprofit organization. The publication appears without any advertising whatsoever and will be published quarterly. Its financial support, except for subscriptions, is derived entirely from a grant given by the United States Public Health Service. The editor, Dr. D. B. Zilversmit of the University of Tennessee, points out that the periodical will represent not only American but also foreign workers in this field and thus will serve to advance its specialty throughout the world.

The technology of medicine is advancing so rapidly, particularly in the field of biochemistry, that workers are finding more and more necessary the development of special publications of limited character.

MORRIS FISHBEIN

ANOTHER REJUVENATOR

IN November 1959 a Professor Aslan appeared in Great Britain to lecture at Apothecary's Hall about her alleged discovery that injections of procaine or NOVOCAIN® had remarkable qualities in rejuvenating the aged. Shortly afterward, a mixture called Gerioptil appeared on the market in Great Britain; this product came originally from West Germany and was alleged to be the one that Professor Aslan was promoting. Subsequently the Professor said that she used only procaine, that the mixture was unknown to her, and that her name had been used by the makers without her permission. The odd mixture contains:

Novocain hydrochloride	2 per cent
Vitamin B_1	5 mg.
Vitamin B_2	2 mg.
Vitamin B_6	2.5 mg.
Niacinamide	20 mg.
Sodium pantothenate	3 mg.
Inositol	10 mg.
Vitamin C	450 mg.
Para-aminobenzoic acid	20 mg.

Apparently little evidence is offered of any real virtues of Gerioptil, except that two physicians say they found it helpful in intractable cases of rheumatoid arthritis and in parkinsonism. The total experience with it seems to have been in two cases of rheumatoid arthritis and two patients with Parkinson's disease.

According to the *British Medical Journal*, a course of treatment with Gerioptil includes 12 injections and 12 ampules and costs £2.10

(roughly $7.00) less the doctor's discount of 15 per cent.

Nothing resembling any real scientific evidence has been offered in support of either procaine alone, which peculiarly is called H_3 by Professor Aslan, or Gerioptil, which is obviously an attempt to capitalize on her publicity. The editor of the *British Medical Journal*, who has the courage of his convictions, says simply, "Whatever substance there may be in Professor Aslan's observations, her published papers and her recent lectures in London fail to disclose any scientifically valid evidence in support of her conclusions."

Already a few references to this technic have appeared in some American newspapers and periodicals. Knowledge of the technics of promoters of such proprietary products warrants the early publication of this statement in anticipation that H_3, Gerioptil, or something equally worthless will soon appear on the American market.

MORRIS FISHBEIN

REFERENCES

EDITORIAL: H_3 developments. Brit. M. J. 2:1317 (December 12) 1959.
GILLHESPY, R. O. and CHATTERJEE, A. K.: H_3. *Ibid.*, p. 1334.

A NEW TECHNIC FOR TREATING PELVIC CANCER

THE use of nitrogen mustard and allied compounds in the treatment of cancer has been necessarily limited by the toxicity of these drugs and the potential damage to normal tissues, particularly those of the gastrointestinal tract and the blood-forming organs. In the departments of surgery and medicine of the Massachusetts General Hospital and the Harvard Medical School, under grants from the United States Public Health Service and the American Cancer Society, a study[1] has been carried out on the treatment of malignant pelvic tumors by extracorporeal perfusion with chemotherapeutic agents. Creech and his associates developed the technic of minimizing systemic toxicity and preventing high levels of alkylating agent in the tumor and its immediate surroundings by isolating the circulation of a region bearing the tumor and perfusing it by a method which utilizes an extracorporeal circuit. An oxygenator is incorporated into the perfusion circuit to increase the effect of the radiomimetic agents, since it has been shown that radiation is more effective at high-oxygen tissue tensions.

Obviously, the technic can be employed only in institutions where all of the necessary equipment and safeguards are available. In their report, Dr. Austen and his associates[1] describe seven cases which were treated by this technic. They note that fractionated intra-arterial administration of nitrogen mustard can be combined with a standard course of radiation therapy without evidence of overdosage to the tissues involved. This has increased effectiveness against tumors. Tumor regression in four of the seven cases was encouraging evidence that pelvic perfusion can be a successful adjunct in the palliative management of pelvic cancer.

The development of new technics for the attack on cancer has been intensified and is approaching a point of practical application.

MORRIS FISHBEIN

REFERENCE

1. AUSTEN, W. GERALD ET AL.: Treatment of malignant pelvic tumors by extracorporeal perfusion with chemotherapeutic agents. New England J. Med. 261: 1037-1045 (November 19) 1959.

THE AGED IN THE NETHERLANDS

STATISTICS for the years 1951 to 1959 indicate that in the Netherlands there were 58 persons 100 years of age or older. Twenty-two were men and 36 were women. Twenty-seven of these were 100 years of age, 11 were 101, three were 102, five were 103, six were 104, two were 105, one was 106, and two were 107. One person was 109 years of age. Of the total number, 30 were widows and 21 were widowers; seven were single. The total population of the Netherlands is 11.25 million; hence, the number of persons per million who were 100 years of age or older would be between five and six.

MORRIS FISHBEIN

relieves both stiffness and pain with safety... sustained effect

In 100 consecutive patients with the low back syndrome, Kestler[1] reported that particularly gratifying was the ability of SOMA "to relax muscular spasm, relieve pain, and restore normal movement, thus speeding recovery in a large majority of the patients."

RESULTS WITH SOMA IN THE LOW BACK SYNDROME*

*Investigators' reports to the Medical Department, Wallace Laboratories. (Total of 278 cases)

NOTABLE SAFETY—extremely low toxicity; no known contraindications; side effects are rare; drowsiness may occur, usually at higher dosage

RAPID ACTION—starts to act quickly **SUSTAINED EFFECT**—relief lasts up to 6 hours

EASY TO USE—usual adult dosage is one 350 mg. tablet 3 times daily and at bedtime

SUPPLIED—as white, coated, 350 mg. tablets, bottles of 50; also available for pediatric use: 250 mg., orange capsules, bottles of 50

1. Kestler, O.: In The Pharmacology and Clinical Usefulness of Carisoprodol, Wayne State University Press, Detroit, 1959. 2. Berger, F. M.; Kletzkin, M.; Ludwig, B. J.; Margolin, S., and Powell, L. S.: J. Pharm. Exp. Ther. *127*:66 (Sept.) 1959. 3. Spears, C. E. and Phelps, W. M.: Arch. Pediat. *76*:287 (July) 1959. 4. Phelps, W. M.: Arch. Pediat. *76*:243 (June) 1959. 5. Friedman, A. P.; Frankel, K., and Fransway, R. L.: Papers presented at Scientific Meeting, New York State Society of Industrial Medicine, Inc., New York, Sept. 30, 1959. 6. Kuge, T.: Unpublished reports. 7. Ostrowski, J. P.: Orthopedics *2*:7 (Jan.) 1960.

Literature and samples on request

Also available on request: The Pharmacology and Clinical Usefulness of Carisoprodol, Wayne State University Press, Detroit, 1959. (185 pages)

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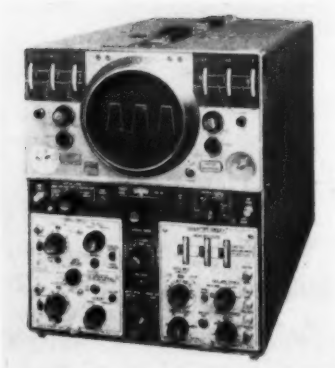

• OSCILLOSCOPE
(Model 425)

DESCRIPTION: Incorporating a direct digital reading system, this instrument also features modular construction, a series of interchangeable plug-in amplifiers, and a new cathode ray tube. It may be used by workers without any technical training. The cathode ray tube has an acceleration potential of 12,000 V. The unit weighs 125 lb., measures 27 by 13½ by 16½ in., and requires 1000 W at 60 cps, 115 V. It is ventilated by forced filtered air and can be operated from 48 through 450 cps by using an optional motor.
PRODUCER: Allen B. Du Mont Laboratories, Inc., Clifton, N. J.

• PRINADOL

PURPOSE: Narcotic-analgesic.
COMPOSITION: Phenazocine.
CAUTION: Contraindicated in cases of severe hepatic insufficiency, severe central nervous system depression or coma, increased intracranial pressure, myxedema, acute alcoholism, delirium tremens, and convulsive disorders. Physicians should be alert for signs of respiratory depression with intravenous administration of Prinadol, especially if the patient has emphysema or other pulmonary disease.
DOSAGE AND ADMINISTRATION: Usual optimal single intramuscular dose is 2 mg. Dosage should be adjusted according to the severity of pain and the patient's response.
HOW SUPPLIED: 1 cc. ampules and 10 cc. vials.
PRODUCER: Smith Kline & French Laboratories, Philadelphia.

• MIRADON TABLETS

PURPOSE: Long-term anticoagulant therapy.
COMPOSITION: Each tablet contains 50 mg. 2-p-anisyl indandione-1, 3.
HOW SUPPLIED: Bottles of 100.
PRODUCER: Schering Corporation, Bloomfield, N. J.

(Continued on page A-140)

asleep minutes after

This is the promise of Noludar 300... a night of deep, refreshing sleep without risk of habituation or toxicity... 6 to 8 hours of undisturbed rest... an easy awakening in the morning, free of fogginess or barbiturate "hangover." Try Noludar 300 for your next patient with a sleep problem. One capsule at bedtime. Chances are she'll tell you

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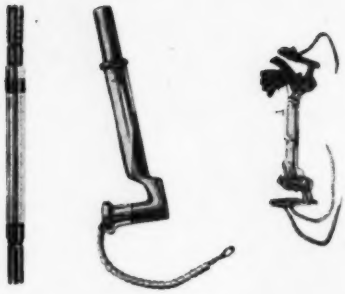


• MEDICAL LAMPS

DESCRIPTION: Combined with the 21 basic lamps in this line are more than 100 variations of 16 types of radiant heater tubes and fixtures. Also provided are heavy-duty extruded aluminum fixtures and 16 basic quartz immersion heaters, of which over 50 variations may be obtained.
PRODUCER: Quartz Radiation Corporation, Newark.

• CYNAL

PURPOSE: Nutritional therapy.
COMPOSITION: Each cherry-flavored tablet contains vitamins B_{12}, B_1 and B_6.
DOSAGE AND ADMINISTRATION: 1 tablet daily.
HOW SUPPLIED: Bottles of 50.
PRODUCER: Lloyd Brothers, Inc., Cincinnati.

• PROLIXIN ELIXIR
(New Product Form)

DESCRIPTION: This phenothiazine derivative for treatment of mental disorders is now supplied as an elixir in 60 cc. and 16 oz. bottles. The 60 cc. package contains a calibrated dropper.
PRODUCER: E. R. Squibb & Sons, division of Olin Mathieson Chemical Corporation, New York.

• ALDACTONE®

PURPOSE: To treat edema and ascites.
COMPOSITION: Each tablet contains 100 mg. spironolactone.
DOSAGE AND ADMINISTRATION: For adults, 400 mg. daily in divided doses, adjusted according to patient's needs.
HOW SUPPLIED: Bottles of 20 and 100.
PRODUCER: G. D. Searle & Co., Chicago.

• DECAGESIC

PURPOSE: To treat pain that is associated with inflammation.
COMPOSITION: Each tablet contains:

Dexamethasone	0.25 mg.
Acetylsalicylic acid	500 mg.
Aluminum hydroxide in a dried gel	75 mg.

HOW SUPPLIED: Bottles of 100.
PRODUCER: Merck Sharp & Dohme, division of Merck & Co., Inc., Philadelphia.

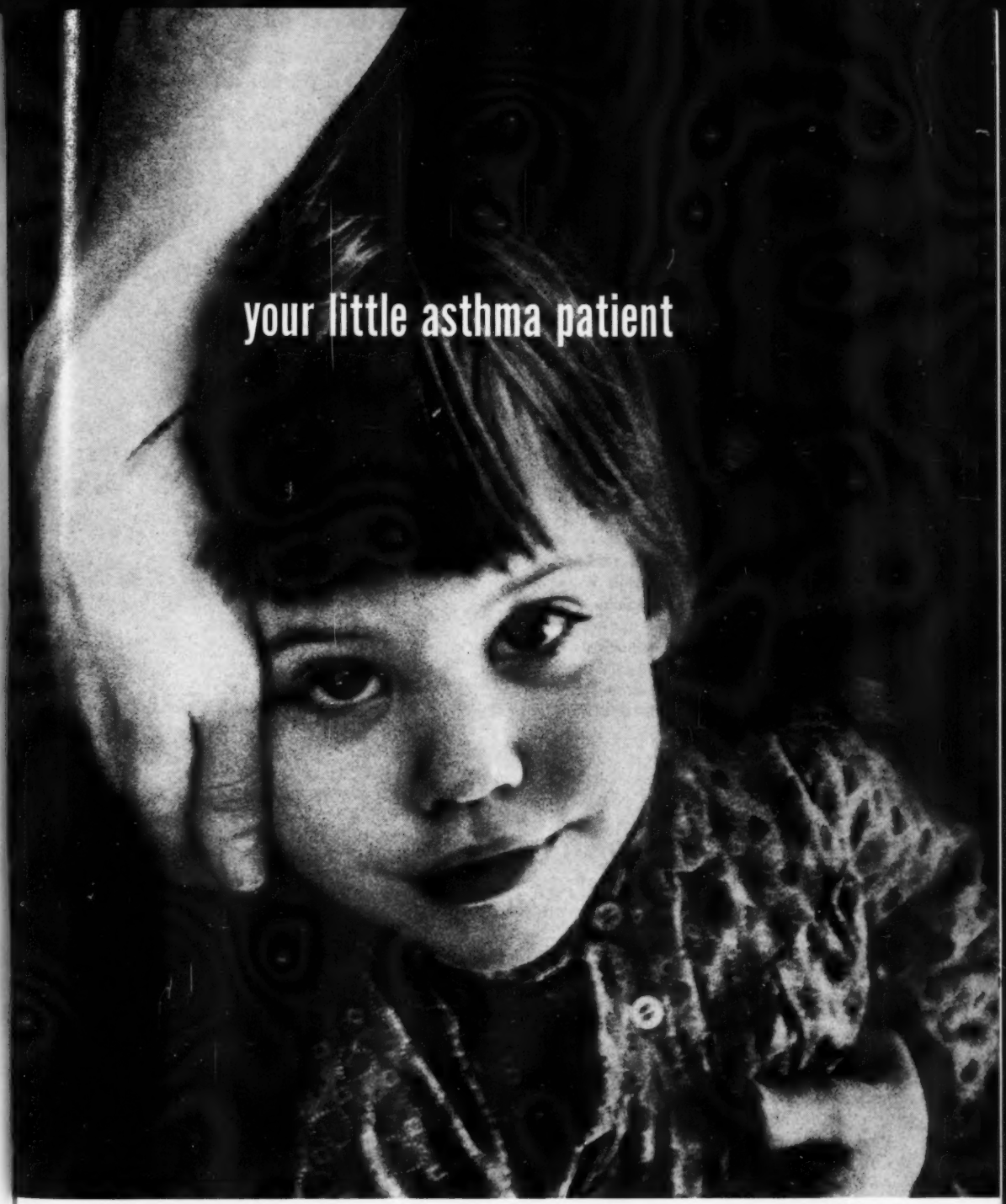
• SYNEX AND SYNEX-SA

PURPOSE: Antihistamine and decongestant.
INDICATIONS FOR USE: Nasal and sinus congestion. Synex-SA is used when pain or discomfort accompanies such conditions.
DOSAGE AND ADMINISTRATION: 1 or 2 capsules four times daily.
PRODUCER: Philadelphia Ampoule Laboratories, Philadelphia.

• ANIMAL CAGE
(Model S-G)

DESCRIPTION: Constructed of stainless steel in the lower section and Galvanneal in the upper part, this cage has rounded inner edges and corners for easy cleaning. The gate is removable and is available in stainless steel or chrome plating. The reinforced frame of the cage has predrilled holes for easy installation. This model comes in six sizes, from 24 by 30 by 30 in. through 48 by 36 by 30 in. (width, height and depth, respectively).
PRODUCER: Animal Cage Specialties Company, Oak Park, Ill.

(Continued on page A-142)



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you can provide it with a single, convenient tablet of NEPHENALIN® PEDIATRIC. Placed under the tongue, NEPHENALIN PEDIATRIC releases isoproterenol HCl, 5 mg., potent epinephrine homologue, to open the airway with utmost speed. Swallowed, the small square red tablet gives the child sustained asthma relief with the well-known, reliable combination of theophylline (1½ gr.), ephedrine (3/16 gr.) and phenobarbital (⅛ gr.). NEPHENALIN PEDIATRIC is available for your prescription in bottles of 20 and 100 tablets. Also available: NEPHENALIN (for adults).

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Nephenalin®

• DYMO-MITE LABELER

DESCRIPTION: Portable and easily operated, this machine embosses labels on metal and plastic tapes. The tape automatically feeds from a roll in the handle to the embossing head. Letters or numbers are selected by rotating the embossing dial. A built-in blade cuts finished labels to any desired length. The tapes have pressure-sensitive backings for permanent application on almost any clean, smooth surface. Plastic tapes are embossed with white letters on one of four colored backgrounds. The aluminum tapes will withstand heat sterilization. Both tapes may be manually removed without damage to the under surface.
PRODUCER: Rehabilitation Products, division of American Hospital Supply Corp., Evanston, Ill.

• STREP-DICRYSTICIN

PURPOSE: Antibiotic.
COMPOSITION: Streptomycin.
HOW SUPPLIED: Sterile powder in one-dose and five-dose vials, to be reconstituted with 1.5 cc. and 7 cc. diluent, respectively.
PRODUCER: E. R. Squibb & Sons, division of Olin Mathieson Chemical Corporation, New York.

• NOVAHISTINE® SINGLET TABLETS

PURPOSE: To relieve symptoms of colds and sinusitis.
COMPOSITION: Each tablet contains:

Phenylephrine hydrochloride	40 mg.
Chlorprophenpyridamine maleate	8 mg.
APAP (N-acetyl-para-aminophenol)	500 mg.

DOSAGE AND ADMINISTRATION: 1 tablet three times daily.
HOW SUPPLIED: Bottles of 50.
PRODUCER: Pitman-Moore Co., Indianapolis.

• ORETICYL®

PURPOSE: Antihypertensive agent.
COMPOSITION: Each tablet of Oreticyl 25 contains 25 mg. hydrochlorothiazide (ORETIC®) and 0.125 mg. deserpidine (HARMONYL®); each tablet of Oreticyl 50 contains 50 mg. hydrochlorothiazide and 0.125 mg. deserpidine; and each tablet of Oreticyl Forte contains 25 mg. hydrochlorothiazide and 0.25 mg. deserpidine.
CAUTION: Patients should be observed for early signs of dehydration or electrolyte imbalance. Nasal stuffiness, drowsiness or lethargy may occasionally occur, but usually can be controlled by adjusting the dosage.
DOSAGE AND ADMINISTRATION: At the start of treatment, 1 to 4 tablets Oreticyl Forte daily. After the patient's condition has become stabilized, Oreticyl Forte in a reduced dosage, Oreticyl 25, or Oreticyl 50 may be given.
HOW SUPPLIED: Bottles of 100 and 1000.
PRODUCER: Abbott Laboratories, North Chicago.

• BACID®

PURPOSE: To treat postantibiotic diarrhea.
COMPOSITION: Each capsule contains a human strain of viable *Lactobacillus acidophilus* and 100 mg. sodium carboxymethylcellulose.
DOSAGE AND ADMINISTRATION: 2 capsules two to four times a day, preferably with milk.
HOW SUPPLIED: Bottles of 50.
PRODUCER: U. S. Vitamin & Pharmaceutical Corp., New York.

• ISOGESIC

PURPOSE: Decongestive, antihistaminic and analgesic agent.
COMPOSITION: Each tablet contains:

d-Isoephedrine HCl	25 mg.
Chlorpheniramine maleate	2 mg.
Salicylamide	150 mg.
N-acetyl-p-aminophenol	150 mg.

CAUTION: Contraindicated in patients with severe hypertension or cardiac disease.
DOSAGE AND ADMINISTRATION: 1 or 2 tablets every three or four hours.
HOW SUPPLIED: Bottles of 100 and 1000.
PRODUCER: Arnar-Stone Laboratories, Inc., Mount Prospect, Ill.

(Continued on page A-144)

CONSISTENT RESPONSE IN VAGINITIS

THROUGH HIGH ANTIBACTERIAL AND ANTITRICHOMONAL EFFECTS, RAPID DIFFUSION, PROLONGED RETENTION

85% SUCCESS:[1,2] TRIBURON VAGINAL CREAM ACHIEVED SYMPTOMATIC CONTROL IN 109 OF 128 WOMEN WITH TRICHOMONAL, MONILIAL AND NON-SPECIFIC VAGINITIS. PARTICULARLY GOOD RESULTS WERE OBTAINED IN TRICHOMONAL AND MIXED INFECTIONS. ONLY TWO INSTANCES OF TRANSIENT BURNING OCCURRED, AND ONLY 11 RECURRENCES WERE NOTED. FURTHER, THE ACTIVE COMPONENT OF TRIBURON VAGINAL CREAM, TRICLOBISONIUM CHLORIDE, HAS BEEN PROVED "NON-IRRITATING...NOT SENSITIZING."[3]

TRIBURON VAGINAL CREAM—FOR VULVITIS AND VAGINITIS DUE TO TRICHOMONAS VAGINALIS, CANDIDA ALBICANS, HEMOPHILUS VAGINALIS AS WELL AS MIXED INFECTIONS; AFTER CAUTERIZATION, CONIZATION AND IRRADIATION; FOR SURGICAL AND POSTPARTUM TREATMENT. THERAPY MAY BE CONTINUED DURING PREGNANCY AND MENSTRUATION.

HIGHLY ACCEPTABLE TO PATIENTS

TRIBURON VAGINAL CREAM—A SMOOTH, WHITE, NONSTAINING PREPARATION WITH NO HINT OF MEDICINAL ODOR—HAS THE ADVANTAGES OF CONVENIENT BEDTIME ADMINISTRATION AND OF DISPOSABLE APPLICATORS.

SUPPLIED: 3-OUNCE TUBE WITH 18 DISPOSABLE APPLICATORS.

REFERENCES: 1. N. MULLA AND J. J. McDONOUGH, ANN. NEW YORK ACAD. SC., 82:(ART. 1), 182, 1959. 2. L. E. SAVEL, D. B. GERSHENFELD, J. FINKEL AND P. DRUCKER, IBID., P. 186. 3. R. C. V. ROBINSON AND L. E. HARMON, ANTIBIOTICS ANNUAL 1958-1959, NEW YORK, MEDICAL ENCYCLOPEDIA, INC., 1959, P. 113.

TRIBURON® CHLORIDE

ROCHE LABORATORIES
DIVISION OF HOFFMANN-LA ROCHE INC
NUTLEY 10, N. J.

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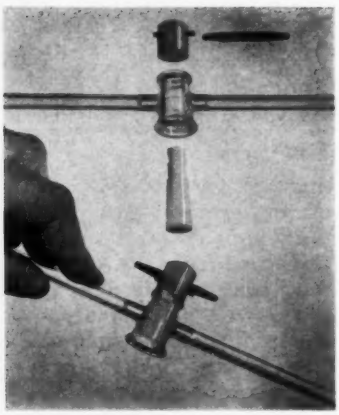
decisive microbicidal therapy
in a delicate matter
not an antibiotic • not a nitrofuran



• THREADLESS STOPCOCK PLUG

DESCRIPTION: Made of corrosion-resistant TEFLON®, this plug has a reverse taper design that eliminates the need for a screw thread. Designed for laboratory apparatus such as burets and separator funnels, the plug has a bore size of 2 mm. It is self-adjusting to temperature changes, will not freeze, and requires no lubrication. A constant-tension spring holds the plug in place. A nylon cap prevents accidental dislodging and reduces spring exposure to a minimum.
PRODUCER: Corning Glass Works, Corning, N.Y.

• HASANONE® NO. 2

PURPOSE: Antitussive and expectorant.
COMPOSITION: Each 30 cc. contains:

Dihydrocodeinone bitartrate	10 mg.
Chlorpheniramine maleate	12 mg.
d-Isoephedrine hydrochloride	75 mg.
Glyceryl guaiacolate	500 mg.
Sodium citrate	972 mg.
Citric acid	324 mg.
Chloroform	2 min.
Aromatized syrupy vehicle	q.s.
Benzoic acid	0.1%
Alcohol, by volume	5%

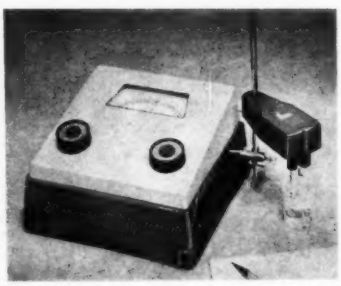
CAUTION: Administer with caution to patients with hypertension, cardiorenal disease or hyperthyroidism.
DOSAGE AND ADMINISTRATION: Adults, 1 or 2 teaspoonfuls three to four times a day; children age 6 to 12, one-half adult dosage.
HOW SUPPLIED: 4 oz., 1 pt. and 1 gal. bottles.
PRODUCER: Charles C. Haskell & Company, Richmond, Va.

• THERABILE®

PURPOSE: To treat noncalculous disease and postoperative disorders of the gallbladder and to support over-all digestive function.
COMPOSITION: Ferrated ox bile, desoxycholic acid, methionine, pancreatin, homatropine methylbromide and oleoresin ginger.
DOSAGE AND ADMINISTRATION: 1 tablet three times daily.
HOW SUPPLIED: Bottles of 100 and 500.
PRODUCER: B. F. Ascher & Company, Inc., Kansas City, Mo.

• TIGAN® TIMESPAN TABLETS
(New Dosage Form)

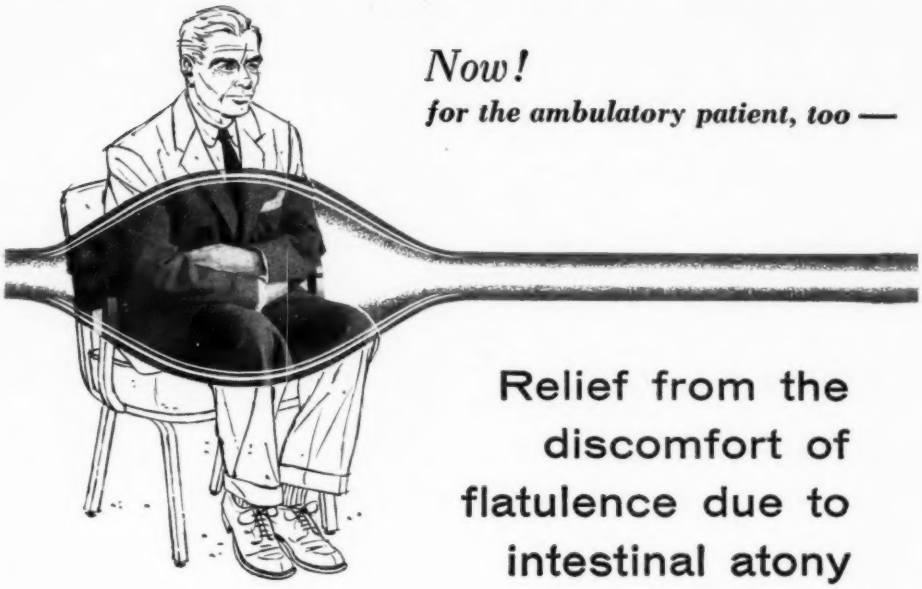
PURPOSE: Antiemetic.
COMPOSITION: Each long-acting tablet contains 300 mg. Tigan hydrochloride.
DOSAGE AND ADMINISTRATION: For pregnant patients, 2 tablets at bedtime and, in severe cases of nausea and vomiting, 1 or 2 tablets on arising. For other adult patients, 1 or 2 tablets twice daily.
HOW SUPPLIED: Packages of 50 and 500.
PRODUCER: Roche Laboratories, Division of Hoffmann-La Roche, Inc., Nutley, N. J.



• METRION pH METER

DESCRIPTION: Providing high precision and an extended range, this instrument utilizes large, clear, duplex scales covering 0 to 10.0 and 4.0 to 14.0 pH. A convenient electrode mounting system adapts to titrations and a wide range of sample volumes. The case is resistant to shock, acids and stains.
PRODUCER: Coleman Instruments, Inc., Maywood, Ill.

(Continued on page A-146)



Now!

for the ambulatory patient, too —

Relief from the discomfort of flatulence due to intestinal atony

WARREN-TEED

ILOPAN®-CHOLINE *tablets*

The successful use of parenteral ILOPAN, in thousands of hospitals, for prevention and relief of post-surgical retention of flatus and feces, has brought demands for similarly effective medication for ambulatory patients — those suffering from intestinal atonia and/or gas retention, as such or as complications of geriatric problems, gastric hyperacidity, gastritis, pregnancy, irritable colon, ureteroenterostomy, regional ileitis, splenic flexure syndrome, infectious hepatitis, cholecystitis.

To ILOPAN (brand of d-pantothenyl alcohol) which aids formation of coenzyme A (essential to acetylation of choline) has been added Choline, the parent substance of acetylcholine (necessary for gastrointestinal tonus). *Effectiveness? — 90% in three independent clinical evaluations of patients of all ages from 20 to 80! And safe.*

COMPOSITION: Each tablet contains Ilopan (brand of d-pantothenyl alcohol) 50 mg., choline bitartrate 25 mg.

INDICATIONS: Gas retention in the atonic gastrointestinal tract of ambulatory patients.

DOSAGE: Two tablets three times daily. Three tablets three times daily in severe cases.

HOW SUPPLIED: Bottles of 100 and 500.

WARREN-TEED PHARMACEUTICALS

THE WARREN-TEED PRODUCTS COMPANY

COLUMBUS 8, OHIO

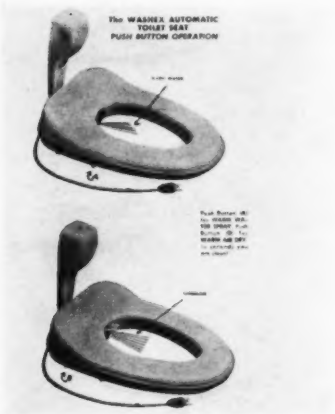
Dallas Chattanooga Los Angeles Portland

• QUADRINAL SUSPENSION

PURPOSE: Bronchodilator and expectorant.
COMPOSITION: Each teaspoonful contains:

Ephedrine hydrochloride	12 mg.
Phenobarbital	12 mg.
Theophylline calcium salicylate	65 mg.
Potassium iodide	160 mg.

CAUTION: Use with caution in cases of sensitivity to iodides, hyperthyroidism and cardiovascular disease.
DOSAGE AND ADMINISTRATION: Adults and children more than 12 years of age, 2 teaspoonfuls three times a day; children 6 to 12 years old, 1 teaspoonful three times a day; children less than six, adjust dose according to body weight.
HOW SUPPLIED: 1 pt. bottles.
PRODUCER: Knoll Pharmaceutical Company, Orange, N. J.



• WASHEX AUTOMATIC TOILET SEAT

DESCRIPTION: Automatically operated by push button or foot switch, this toilet seat gently cleanses the rectal and vaginal areas with a warm water spray (A) and provides thorough drying with warm air (B). It eliminates perineal and hemorrhoidal irritations, cross infection, and other problems resulting from the use of toilet tissue; it also is ideal for handicapped patients. Temperature, air and spray pressure are automatically controlled; water and air are heated only when the seat is in use.
PRODUCER: Rehabilitation Products, division of American Hospital Supply Corporation, Evanston, Ill.

• MODUMATE®

PURPOSE: To treat ammonia intoxication due to hepatic failure.
COMPOSITION: Each 100 ml. of Modumate solution provides 13.5 gm. L-arginine and 12 gm. L-glutamic acid (including 0.5 gm. excess glutamic acid).
CAUTION: This drug is not recommended for managing hepatic disorders in which blood levels of ammonia are relatively normal. Fluid and electrolyte balance should be maintained at all times and supportive measures should be instituted when needed.
DOSAGE AND ADMINISTRATION: Dilute 100 ml. of Modumate with 500 or 1000 ml. of 5 or 10 per cent dextrose. Administer an initial dose of 25 to 50 gm. by intravenous infusion over a period of not less than one hour for 25 gm. and not less than two hours for 50 gm. Repeat after eight hours if blood levels of ammonia are still increased or if coma persists. Severe cases may require repeated infusions for three to five days.
HOW SUPPLIED: 25 per cent (w/v) Modumate solution in water in 100 ml. sterile containers, packed individually or in cartons of six.
PRODUCER: Abbott Laboratories, North Chicago.

• INLAY-TAB®

DESCRIPTION: Consisting of a recessed outer shell into which a smaller tablet is inlaid, this new medication form allows two incompatible components to be combined in a single tablet. The Inlay-Tab also can be used for timed-release and sustained-release medications.
PRODUCER: Smith-Dorsey, a division of The Wander Company, Lincoln.

• LIBRIUM

PURPOSE: To alleviate anxiety and tension states.
COMPOSITION: 7-chloro-2-methylamino-5-phenyl-3H-1, 4-benzodiazepine 4-oxide hydrochloride.
DOSAGE AND ADMINISTRATION: A low dosage is indicated in mild to moderate anxiety and tension; a higher dosage is given in more severe tension states, chronic alcoholism, agitated depression and ambulatory psychoneuroses.
HOW SUPPLIED: 10 mg. capsules in bottles of 50 and 500.
PRODUCER: Roche Laboratories, Division of Hoffmann-La Roche, Inc., Nutley, N. J.

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APRIL 1960

If You Want To Buy A Marketable U.S. Security - how do you go about making purchase? Yields of around 5% have attracted the investment interest of many individuals who formerly limited purchase of any U.S. securities to savings bonds. Now, considering buying such securities for the first time, they are uncertain as to how purchase can be made.

If you are considering purchase of a new U.S. issue, simplest procedure is to handle it through your bank. Many banks make only a nominal charge to a customer, and in some instances charge nothing for their service. You can also place an order to buy a new issue of a Government security in person with a Federal Reserve Bank or a branch bank of the Federal Reserve.

When you wish to buy a marketable U.S. security already outstanding, you can have your bank handle your order. Or you can buy through a broker. In either case, you will have to pay a commission. These marketable Government securities usually are traded in denominations of $1,000 and up.

Treasury Bills And Notes - are those issues which have attracted greatest attention from individuals making this type of investment for the first time. These bills and notes differ in the method of giving a return to the investor and also maturity period.

A Treasury bill does not pay interest as such. It gives a return to investor measured by the discount at which it is sold and the amount which will be paid on maturity. Every Monday, bills having a maturity of three and six months are auctioned. Bills with a one year maturity are auctioned every three months. These bills are purchased by large investors such as banks and corporations who submit competitive bids for them. An individual investor can also make a competitive bid but whether he will get some of the bills he seeks will depend upon how the price he offers compares with other bids. However, the more normal procedure is to submit a noncompetitive bid for a certain amount of bills. The investor thus is assured of getting the amount he wants. Here, he

agrees to pay a price equal to the average price resulting from competitive bids by the large investors.

Treasury notes have a longer maturity than bills - 1 to 5 years. They also give fixed interest and are sold at a fixed price on a subscription basis. Subscriptions by investors usually exceed the amount of any one issue. As a result, Treasury notes are apportioned among subscribers. However, full allotment is made on the small subscription by the individual investor - normally up to but not in excess of a $25,000 amount.

* * * * *

At What Age Will You Retire? The doctor retires at an older age than the average executive or other individual employed by business. Retirement age in business now is generally geared to 65. However, retirement age for 80% of U.S. doctors is about 72.

Charitable Aid For Hospitals - gets Internal Revenue Service assistance. Favorable rulings also have opened the way for a doctor to couple charitable contribution with savings for his retirement. Previously, the Service approved the fund-raising method using the tax-free life income contract for a number of colleges. Now it has extended its favorable ruling to other tax-exempt organizations - in its latest ruling, to the plan of Johns Hopkins Hospital. What are the advantages of this type of plan to potential donors?

Under these plans, a donor can give appreciated securities to institution. On sale of securities, he would have capital gain - which is avoided on gift. The institution converts the security gift to tax-exempt municipal bonds. Interest on bonds paid to donor is tax free. On the donor's death, the bonds become absolute property of institution. The donor thus is giving a remainder interest to the institution. He's entitled to current charitable deduction for value of such interest - to reduce current taxable income.

How could this plan work out in practice? Income of a doctor, now age 67, will drop substantially from current $25,000 a year when he retires. A number of years back, he purchased stock for $2,000 which is now worth $10,000. He gives the stock to an institution, such as his university or a hospital, in return for a tax-free life income contract. The institution reinvests his gift in tax-exempts, yielding 3.5% for an annual tax-free return of $350. On gift, the doctor gets a charitable deduction of $6,900. In his tax bracket, that is worth $3,000. So he's actually made an investment of $7,000 ($10,000 stock value less $3,000 tax savings). A $350 annual return on $7,000 gives a tax-free yield

of 5%. If the doctor had sold his stock instead and made similar investment directly, he'd incur a capital gains tax. On reduced capital for reinvestment, he'd get an annual return of only $290. That's a return of 2.9% on his original $10,000 capital.

More Retirement Income Can Be Secured - by borrowing against the tax savings produced under a life income contract gift. A donor giving cash or securities in return for a life income contract gets a current charitable deduction for the value of the remainder interest going to the tax-exempt institution on his death.

A doctor, now age 70, has income of $25,000 a year. After retirement, his income will drop. He is holding $7,000 in liquid savings, seeking an investment which promises safety plus maximum return. By making advance use of the tax savings available through a charitable life income contract, the doctor can increase income return. For instance, on a $10,000 gift to his alma mater for a life income contract, he'll get a charitable deduction at his age of $7,260. In his tax bracket, that deduction has a tax value of about $3,200. He borrows $3,200 from a bank. With those borrowings and $6,800 of his own funds, he makes a $10,000 gift for a life income contract. He uses the $3,200 tax savings produced on the gift to pay off his bank loan. While he's actually made an investment of only $6,800 in the life income contract, he gets a return for life on $10,000.

* * * * *

"Have Your Cake And Eat It" - is promised by single premium annuity-life combination used in estate planning. For a single premium, you get two contracts - annuity giving tax-protected return for life - and life insurance payable on your death. You can buy combination even though you're not insurable for a premium slightly in excess of the face amount of the life policy. Its new popularity as estate planning tool comes from (1) Supreme Court decision holding two policies are separate and independent and (2) removal of life insurance from your taxable estate by lifetime gift. Consider how this insurance combination might be used by a doctor whose past savings now require an estate plan.

The doctor, age 65, has income of around $25,000 from his practice and investments. He hopes to continue practice for another five years. He will leave a taxable estate of $400,000 - the larger part to his wife but part to his daughter. To save estate tax, he would give some of his investment capital to his daughter now. However, he wants the investment return as a safeguard against any drop in his professional income. Through an annuity-

insurance combination, he can keep the investment return but make a lifetime gift to his daughter now.

A single premium of $108,000 will buy an annuity paying $2,750 a year and $100,000 insurance. He gives the insurance policy to his daughter with his wife's consent. After gift tax exemption and exclusion, he limits tax on his gift to $500. In effect, his estate plan consumes $108,500 of his capital ($108,000 single premium plus $500 gift tax). Assume that he got a 4% return on $108,500 investment capital. After taxes, he kept only $2,500 of that return. From the tax-protected annuity return, he will keep about $2,500 a year after taxes. On the doctor's death, his daughter gets $100,000 insurance income and estate tax free. If he hadn't bought the annuity-insurance combination but left $108,500 to his daughter, she would get only $76,000 of it after estate tax. So without reducing his own current income return, he is able to increase the amount left to his family after his death - by an extra $24,000 going to his daughter.

* * * * *

In Preparing Your Tax Return This Year - take particular pains. The Internal Revenue Service is using a high-speed electronic system in initial processing of returns. That system is being expanded. As a result, more Service personnel will be released for extensive audit work. There will be more audits. Government statistics confirm that. Last year the Service again increased the number of returns audited - up more than 4% over the preceding year. Deficiencies and additional taxes collected were also up - more than 10%. There is an increasing premium in preparing the accurate return.

4 Out Of 5 Tax Return Audits - result in deficiencies, requiring additional tax payment by taxpayers. A taxpayer called in for an audit often is told that the audit is for purposes of checking the accuracy of his return - it probably will not result in additional tax levy. However, statistics tell a different story. About 80% of the time, audits result in deficiencies and additional tax collection.

The statute of limitations for auditing a return doesn't expire for a minimum period of three years. After filing your tax return, set aside and keep in a safe place tax records used in preparing the return. Tax troubles of many taxpayers on audit stem solely from failure to keep such tax records. At time of audit, they no longer can find them. With them, they could substantiate items appearing upon the return. Without them, they can't. Failure to keep tax records may carry a heavy expense - a tax deficiency.

Now available at cost—$1.50—3-ring loose-leaf binder to hold 24 monthly Lasser reports. Made of blue simulated morocco grain leather; non-soil finish with embossed cushion edge. Send check with name and address to POSTGRADUATE MEDICINE, Essex Building, Minneapolis 3, Minnesota.

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People today—because of advances in medicine and the increasing acceptance of the annual physical examination—are living longer.

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THE MEDICAL *Bookman*

► HUMAN BIOCHEMICAL GENETICS

By H. Harris, M.D., Reader in the Department of Biochemistry, London Hospital Medical College, England. 310 pages with 69 illustrations. 1959, Cambridge University Press, London and New York. $7.00.

Although the concept of inborn errors of metabolism is more than 50 years old, it has been popularized only recently. The first book on this subject, "Inborn Errors of Metabolism," by Archibald E. Garrod, appeared in 1909. At that time only four conditions were attributed to this cause, namely, albinism, alkaptonuria, cystinuria and pentosuria. Dr. Harris's book is a summation of the present-day knowledge of the ever-increasing number of diseases that are being recognized as inborn errors of metabolism.

In this text, discussions of these various abnormalities are grouped under several headings: amino acid metabolism; carbohydrate metabolism; human hemoglobins; blood group substances; plasma proteins; and miscellaneous, which includes porphyria, congenital hyperbilirubinemia, acatalasemia, vitamin D-resistant rickets, hypophosphatasia, diabetes insipidus, hemochromatosis, hyperoxaluria, and gout.

In the first of the two excellent introductory chapters, the author explains the meaning of inborn errors of metabolism and discusses biochemical individuality, chromosomes and genes, and the effect of environment on individuals. The second of these chapters deals with some of the aspects of Mendelian heredity, particularly those associated with the diseases under discussion. The final discussion in the book is on the function of the gene in the normal organism and the way in which abnormal genes produce their particular effects through enzymatic action.

This book is an excellent review of the various diseases now recognized as congenital metabolic disorders. It is important for every physician to become familiar with this concept and the role that heredity plays in the perpetuation of these diseases, because it is obvious that as we gain more insight into the biochemistry of diseases, an increasing number of conditions will come under the heading of inborn errors of metabolism.

R. V. R.

► MANAGEMENT OF THE AGED SURGICAL PATIENT

By Sidney E. Ziffren, M.D., Professor of Surgery, State University of Iowa College of Medicine, Iowa City, with three contributors. 219 pages with 30 illustrations. 1960, The Year Book Publishers, Inc., Chicago. $7.50.

As the average life span of man increases and progress in operative surgery continues, our concepts of the use of surgery in the aged patient also change. The current trend is toward the theory that old age alone is not a contraindication to surgery. Nevertheless, aged people do present special problems in surgery, and this new book summarizes well, from both a practical and a philosophical point of view, the place of surgery in geriatrics.

The author points out that the life span itself has not increased much but that more people are living to be older and thus are boosting the average life span. Figures quoted show that at age 70 life expectancy is over 11 years, which is a

(Continued on page A-173)

point worth considering when a patient of this age has a surgically curable disease. On the other hand, the author feels that radical surgery for cancer requires much thought on the part of the surgeon, particularly because a successful radical operation does not necessarily mean the patient has been helped; he may actually have been given a longer period of misery.

All these points are words of wisdom that should fall on the ears of the younger men, in whom one frequently finds misguided enthusiasm.

About half of the book is concerned with preoperative preparation, anesthesia, conduct of the operation, the postoperative period, and complications. The remainder of the text is on specific problems such as acute conditions in the abdomen, gastrointestinal hemorrhage, and some of the major diseases of the abdomen such as cancer, diverticulitis and biliary tract disease. A fairly long section is presented on arterial disease, trauma and urologic disorders, but there is very little discussion on thoracic surgery and neurosurgery.

Emphasis is on practical aspects in the management of the aged patient. Examples include discussions of what to do for patients with asymptomatic gallbladder disease and the relationship of cardiac disease and abdominal disease and their interrelationships in symptomatology.

Y. S.

► PATHOLOGY OF THE HEART

Edited by S. E. Gould, M.D., Professor of Pathology, Wayne State University College of Medicine, Detroit, with 20 contributors. Ed. 2. 1,138 pages, illustrated. 1960, Charles C Thomas, Springfield, Illinois. $32.50.

With this new edition, it is apparent that a book which embraces all facets of the anatomy, physiology, pathology and surgical management of the heart can be of tremendous value to readers when a group of able men pool their knowledge and present a comprehensive discussion.

Beginning with the history of the pathology of the heart, the subject matter is logically developed to include the anatomy of the heart, the conduction system, physiology, congenital malformations, degenerative changes, diseases of the coronary arteries, rheumatic and nonrheumatic heart disease, parasitic infestations of the heart, injuries of the heart and pericardium, neoplasms, lesions of the aorta, cardiopulmonary diseases, a clinicopathologic correlation, weights and measurements of the heart, and histochemical procedures in the study of heart disease.

Each author of the chapters mentioned has enlarged and brought the material up to date, including references. For example, the chapters on the development of the heart, the adult heart, and the conduction system are supplemented with additional color photographs, good black-and-white reproductions, and excellent photomicrographs.

The reader should give particular attention to the chapter on congenital malformations of the heart and great vessels because of the manner in which it is presented and the correlation with clinical alterations. Almost every phase of the anomalies of the heart and great vessels is presented in a very clear and concise manner.

The editor and contributors are to be congratulated on this excellent contribution on the pathology of the heart. It should be in the possession of every cardiologist and pathologist, and should prove to be of extreme value to every physician.

S. A. L.

► TREATMENT OF CANCER IN CLINICAL PRACTICE

Edited by Peter B. Kunkler, M.D., Radiotherapist, United Birmingham Hospitals, Birmingham, and Anthony J. H. Rains, F.R.C.S., Professor of Surgery, University of London Faculty of Medicine, London, England, with 52 contributors. 821 pages, illustrated. 1959, E. & S. Livingstone Ltd., Edinburgh and London. Distributed by The Williams & Wilkins Company, Baltimore. $19.00.

In my 15 years of reviewing books, this is one of the most outstanding works I have been privileged to read. The editors, together with the excellently qualified contributors, have prepared a most comprehensive volume of 40 chapters on all phases of the treatment of cancer as we know it today. Certainly, Dr. Kunkler and Dr. Rains show very clearly the importance of the hand-in-hand approach of the surgeon and radiotherapist in treating various types of cancer.

Prior to discussing the various sites of cancer and the procedures of treatment, the authors present excellent discussions on the evolution of clinical practice; common principles in treat-

(Continued on page A-174)

ment; the approach to surgical methods and technic; the physics, principles and methods of radiotherapy; chemotherapy of malignant disease; hormonal control; and the results of treatment. The subsequent section begins with a discussion of the skin and concludes with a chapter on the groin.

Perfectly reproduced illustrations have been included wherever they seem necessary. The bibliography at the end of each chapter and the 15 page index with headings in boldface type contribute to the excellence of this volume. I highly recommend it to all practicing and research physicians who wish to understand the various methods used by the radiotherapist and the surgeon in the approach to cancer, as well as to become fully aware of the latest advances in the care and treatment of patients with this disease.

I. P. F.

► OFFICE ORTHOPEDICS

By Lewis Cozen, M.D., Attending Orthopedic Surgeon, Cedars of Lebanon Hospital, Los Angeles. Ed. 3. 430 pages with 321 illustrations. 1959, Lea & Febiger, Philadelphia. $9.50.

The vast amount of medical literature and source books published today has to do with the more complicated technical advances in the various fields of medical endeavor. It is refreshing, therefore, to read a volume devoted to the less complicated features of clinical practice. The third edition of this book fulfills the basic need of a great number of practicing physicians who are daily confronted with disease entities that should be treated either in the office or on an outpatient basis.

The introduction of cortisone and its derivatives, many of which are injectable intraarticularly and into soft-tissue structures, has necessitated a medium for brief dissemination of its value. A discussion of this relatively new concept of treatment, along with its methods of use and ability to give satisfactory results, constitutes a large part of the present edition. Indeed, this subject actually stimulated the production of this book.

Primarily, the value of this monograph is in the simple, easily read, and readily understood details that establish quick reference for anyone whose interest or medical contact lies in the field of orthopedics. It is directed toward the general practitioner and has been edited with skill, contributing information and suggestions for therapy that can be applied with relative ease. The treatment of minor orthopedic ailments has generally been passed over quickly in the medical curricula of schools and other centers of learning. This leaves the physician with little firsthand knowledge for definitive and successful care.

The book contains numerous descriptive drawings and photographs. Its format and method of presentation are the same as those of preceding volumes. Those who have made use of earlier editions will welcome this latest volume; others who have not had this contact can with rapid perusal benefit from the subject material.

E. H. O'P.

► PYELONEPHRITIS

By Fletcher H. Colby, M.D., Consultant, Massachusetts General Hospital, Boston. 214 pages with 95 illustrations. 1959, The Williams & Wilkins Company, Baltimore. $7.50.

This concise, readable review of an important disease was prepared by a urologist for a nonurologic audience. It is not a treatise on the surgical management of pyelonephritis. Instead, it is a broad, factual and sobering account of a disease which may be managed successfully—and hence is benign—in its early phases, but which is often untreatable—and therefore devastating—in its chronic form. Thus the author has emphasized the importance of the early recognition and the prompt, accurate medical and surgical therapy of pyelonephritis.

The text consists of 12 chapters. Acute and chronic pyelonephritis are dealt with separately, emphasizing their differences. There are sections on the incidence and etiology of pyelonephritis and on the treatment of infection of the urinary tract. Chapters dealing separately with pyelonephritis in infancy and childhood, in diabetes and in pregnancy are of special interest. The chapter on pyelonephritis and hypertension includes an appraisal of the relationship of unilateral pyelonephritis with hypertension. In a soul-searching final chapter, the author considers the delicate subject of the urologist's role in initiating and perpetuating infections of the urinary tract. He discusses urologic instrumentation and problems of sterilization of equipment in a candid yet constructive manner.

J. C. B.

(Continued on page A-176)

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► SYSTEMIC LUPUS ERYTHEMATOSUS

Edited by George Baehr, M.D. and Paul Klemperer, M.D., Mount Sinai Hospital, New York. 84 pages, illustrated. 1959, Grune & Stratton, Inc., New York. $3.75.

Systemic lupus erythematosus has long since ceased to be a specialty problem of the dermatologist, who designated it as "lupus erythematosus disseminatus" or "lupus sine lupus" and pondered over it as an "explosive" form of discoid lupus. Today, systemic lupus erythematosus must be reckoned with by all physicians as a differential diagnostic possibility in every tentative or working diagnosis. This disease complex has displaced syphilis as the great impersonator in medical symptomatology, and it is increasingly being discovered in the most complex clinical problems.

This volume on systemic lupus erythematosus was prepared by the Mount Sinai Hospital group under the able editorship of George Baehr and Paul Klemperer, and it will be of great assistance to those who wish to reorient themselves on the present status of this clinical problem. It is obvious that this monograph was written for the very practical purpose not only of aiding the physician to understand better this protean disease process and its pathology but also of assisting him in diagnostic considerations and management of the afflicted patient. It is indeed fitting that this symposium originated with the Mount Sinai Hospital group, since the members of that group, singly and collectively, have contributed so liberally to our knowledge of systemic lupus erythematosus over the last 30 years.

The first paper in the monograph, by A. D. Pollack, on the "Pathology of systemic lupus erythematosus," gives a succinct discussion of the various pathologic findings encountered and points out the elusive nature or actual absence of such signs at necropsy in many instances of the fulminating types of disease. The paper is well illustrated with good photographs. The author also indulges in some provocative theorizing on causation and leaves no doubt that the notion of an immune mechanism of some sort is most appealing to him.

The LE cell phenomenon has engaged the attention of many investigators since its original presentation in 1948, when it was a contribution of morphologic hematology. After the first flurry of investigation as to the mechanics of the production of this phenomenon, as well as to its specificity and clinical dependency, the histochemists and immunologists took over. Gabriel C. Godman discusses very thoroughly "The nature and pathogenic significance of the LE cell phenomenon of systemic lupus erythematosus"; he brings the reader up to date on progress and simplifies a complex and confusing subject.

In the paper, "The blood in systemic lupus erythematosus," Stanley L. Lee and Baruch J. Davis discuss each of the plasma and cellular components as it may be affected in systemic lupus erythematosus. They draw on their own extensive experience and summarize that of other observers, and their observations should be of great help to the clinician. They also discuss the LE cell phenomenon in a manner which may be of great practical importance to clinicians and clinical pathologists who do not want to delve into the more complex immunochemical discussion in Godman's paper.

Saul W. Jarcho, in his contribution, "Clinical features of systemic lupus erythematosus," emphasizes under "diagnosis" the point that "the first diagnostic act should be to *suspect*." He then proceeds to discuss the various systemic manifestations of lupus so that the interested reader should be able to lay aside the book with the benefit of a much keener "index of suspicion" when he is confronted with a diagnostic problem.

It is often forgotten that systemic lupus erythematosus can be a disease of childhood. Donald Gribetz and Walter L. Henley, in their paper, "Systemic lupus erythematosus in childhood," analyzed the histories of 15 children (14 girls and one boy) with the disease. They concluded that the manifestations of the disease in this age group do not differ markedly from those seen in adults.

"The therapy of systemic lupus erythematosus" is well discussed by Louis J. Soffer, who, like most physicians, depends primarily on the use of the corticosteroids as the treatment of choice. The effect of therapy is shown in tabular form, so that the reader may draw his own conclusions from the analysis of a large series of cases. Other agents, particularly the antimalarial drugs, also are briefly discussed. If any criticism of this paper were to be offered, it would concern the omission of comments about other parts of a treatment program.

M. M. H.

(Continued on page A-178)

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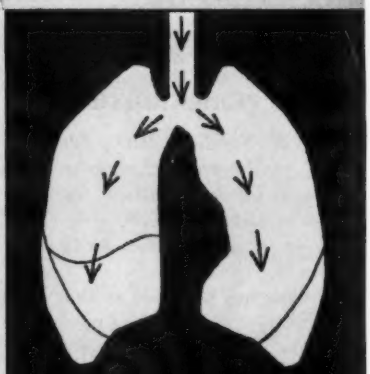

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► THE AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS INSTRUCTIONAL COURSE LECTURES

Edited by Fred C. Reynolds, M.D., St. Louis. Vol. 16. 335 pages with 260 illustrations. 1959, The C. V. Mosby Company, St. Louis. $16.00.

The instructional courses at the annual meeting of the American Academy of Orthopaedic Surgeons have been well attended since their institution in 1943. The present volume of the series presenting most of the subjects handled at the meetings is concerned with injuries to athletes, the hand, the foot, the knee, the spine, unequal extremities, osteomyelitis, electromyography in orthopedic surgery, and fractures of the elbow and femoral neck. Thirty-one nationally known authors have contributed to the discussions. In each instance the coverage of the subject is designed to be as up to date as is possible and to present in great detail both the accepted facts and the attitudes of the author. Adequate bibliographic material is supplied with each part of the book, and the index is good.

The roentgenographic reproductions, photographs, line drawings and graphs serve excellently to augment the text. This is a book which every orthopedic resident and student will find valuable. Also, like others in the series drawn from the instructional courses, it will be of value for the general surgeon who wishes to acquaint himself with some specific phase of orthopedics.

E. W. J.

► ACUTE PERICARDITIS

By David H. Spodick, M.D., Senior Physician and Chief, Cardiographic Laboratory of the Medical Services, Lemuel Shattuck Hospital, Boston. 182 pages, illustrated. 1959, Grune & Stratton, Inc., New York and London. $6.50.

The author has provided in this small volume a comprehensive discussion of modern knowledge of acute pericarditis. In the first part of the text he considers the pericardium and its reaction to inflammation; also included are the anatomy, physiology and pathology of the pericardium, together with descriptions of pain mechanisms and the laboratory and clinical signs of pericarditis. In the second part the author discusses the syndromes of acute pericarditis, including acute nonspecific suppurative and tuberculous pericarditis, the pericarditis associated with viral diseases, the group of connective tissue diseases, and hypersensitivity states.

The chapters on pericardial effusion include detailed discussions of cardiac tamponade, the technics used in pericardial paracentesis, and the x-ray manifestations of pericardial effusion, including angiocardiography and gas cardiography. The final chapter summarizes well the diagnostic features of acute pericarditis and its differentiation from other conditions.

No important subject seems to have been omitted, although one might have expected more information on recurrent acute nonspecific pericarditis and the recent encouraging results of pericardiectomy for this condition.

Dr. Spodick's book is well organized and easily read. It appears to cover more comprehensively than does any other textbook available the details of present knowledge of acute pericarditis, and it can be highly recommended.

D. C. C.

► THE PHARMACOLOGY AND CLINICAL USE OF DIURETICS

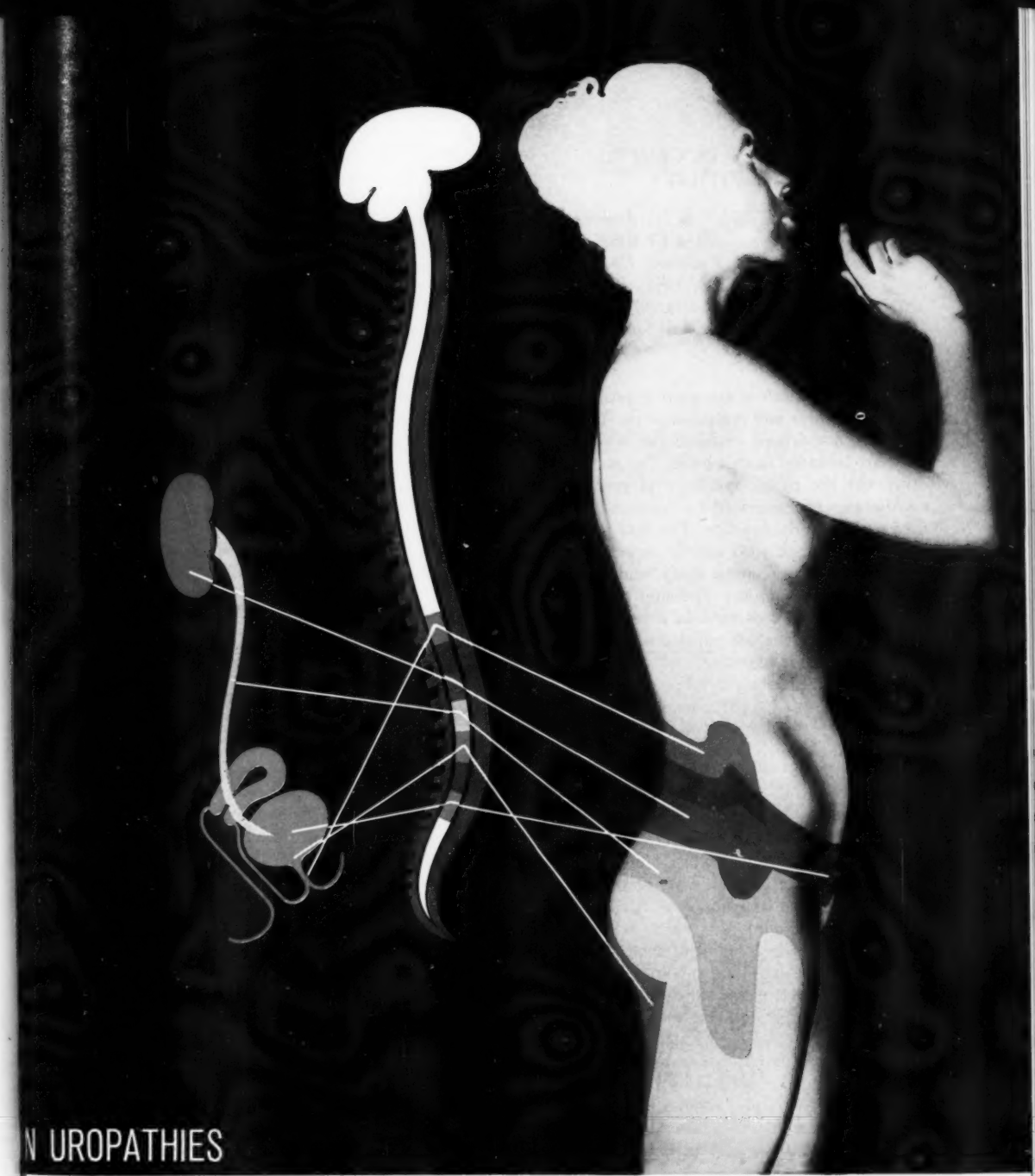
By Carroll A. Handley, Ph.D., Professor of Pharmacology, Baylor University College of Medicine, Houston, and John H. Moyer, M.D., Professor of Internal Medicine, Hahnemann Medical College and Hospital of Philadelphia. American Lecture Series. 194 pages. 1959, Charles C Thomas, Springfield, Illinois. $6.00.

A concise account of each of the five major groups of diuretic agents in use today is given in this well-organized, easy-to-read volume. The opening chapters review current concepts of water and electrolyte balance, the pathophysiology of edema in various disease states, and technics for estimating the potency of diuretic agents. The newer drugs, including those which inhibit the production of aldosterone, are next considered. A final chapter purporting to summarize the clinical use of diuretic agents singly or in combination and in various altered states provides a *reductio ad absurdum* of limited value.

An appendix contains instruction in low-sodium diets. Subject and author indexes and a bibliography are included, and there is a liberal number of figures and tables.

J. C. B.

(Continued on page A-180)



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► DISTURBANCES IN GASTRO-INTESTINAL MOTILITY

Edited by J. Alfred Rider, M.D., Assistant Professor of Medicine, and Hugo C. Moeller, M.D., Assistant Professor of Medicine, University of California School of Medicine, Berkeley-San Francisco, with 28 contributors. 387 pages, illustrated. 1959, Charles C Thomas, Springfield, Illinois. $13.00.

The contributions of the participants in a program of lectures and symposia at the University of California School of Medicine in December 1958 are included in this book. The material encompasses the pathophysiology of gastrointestinal diseases characterized by constipation, diarrhea or biliary dysfunction. The first part of the book is concerned with certain aspects of pertinent physiology, pharmacology and psychodynamics of such disorders. The later portions deal with diagnosis and therapy in a practical, clinical manner, and include panel discussions on ulcerative colitis and constipation.

In the initial chapters, the physiology of normal and abnormal gastrointestinal motility, including current methods of measurement, is discussed. The following sections are devoted to various aspects of diarrhea and constipation, including a general discussion of the pharmacologic principles involved in their management, infectious diarrheas, and diarrhea in the young child. Functional constipation is the subject of a symposium, and a chapter is devoted to the use of newer drugs in its management. Disorders of the gallbladder and biliary tract are discussed also, with attention to clinical features, laboratory and roentgenographic aids in diagnosis, and treatment. Subjects of special chapters are chronic cholecystitis, postcholecystectomy syndromes and biliary dyskinesia. Attempts to study and better define the latter by the technics of serial cholecystography, as well as by operative manometry and radiography, are described in detail. There are also chapters on acute gastric dilatation and paralytic ileus, regional enteritis, and postgastrectomy syndromes.

One of the best sections is that dealing with motility disturbances associated with systemic disease. Normal and abnormal motility in various parts of the gastrointestinal tract in a number of diseases is presented, and the effects of some drugs on motor activity and the practical implications of such knowledge are considered.

There is considerable unevenness in the style, level of scientific approach, and intrinsic value of the various contributions in this book. Its title is misleading, since it suggests that disordered gastrointestinal motility is the etiologic basis of the diseases covered in the book rather than an arbitrarily selected and at times tangential approach to them. Actually, motility per se is discussed only sporadically and does not serve adequately as the unifying concept of the volume. Certain sections, namely, those in which the pharmacology and therapy of constipation are discussed, seem to reflect unduly the support given the program by a pharmaceutical house.

Nevertheless, this book has practical and useful parts, and should be informative to those who wish to know more in a general way about clinical aspects, diagnosis and therapy of a number of the more common and important gastrointestinal problems.

H. N. H.

► BABIES BY CHOICE OR BY CHANCE

By Alan F. Guttmacher, M.D. 289 pages. 1959, Doubleday & Company, Inc., Garden City, New York. $3.95.

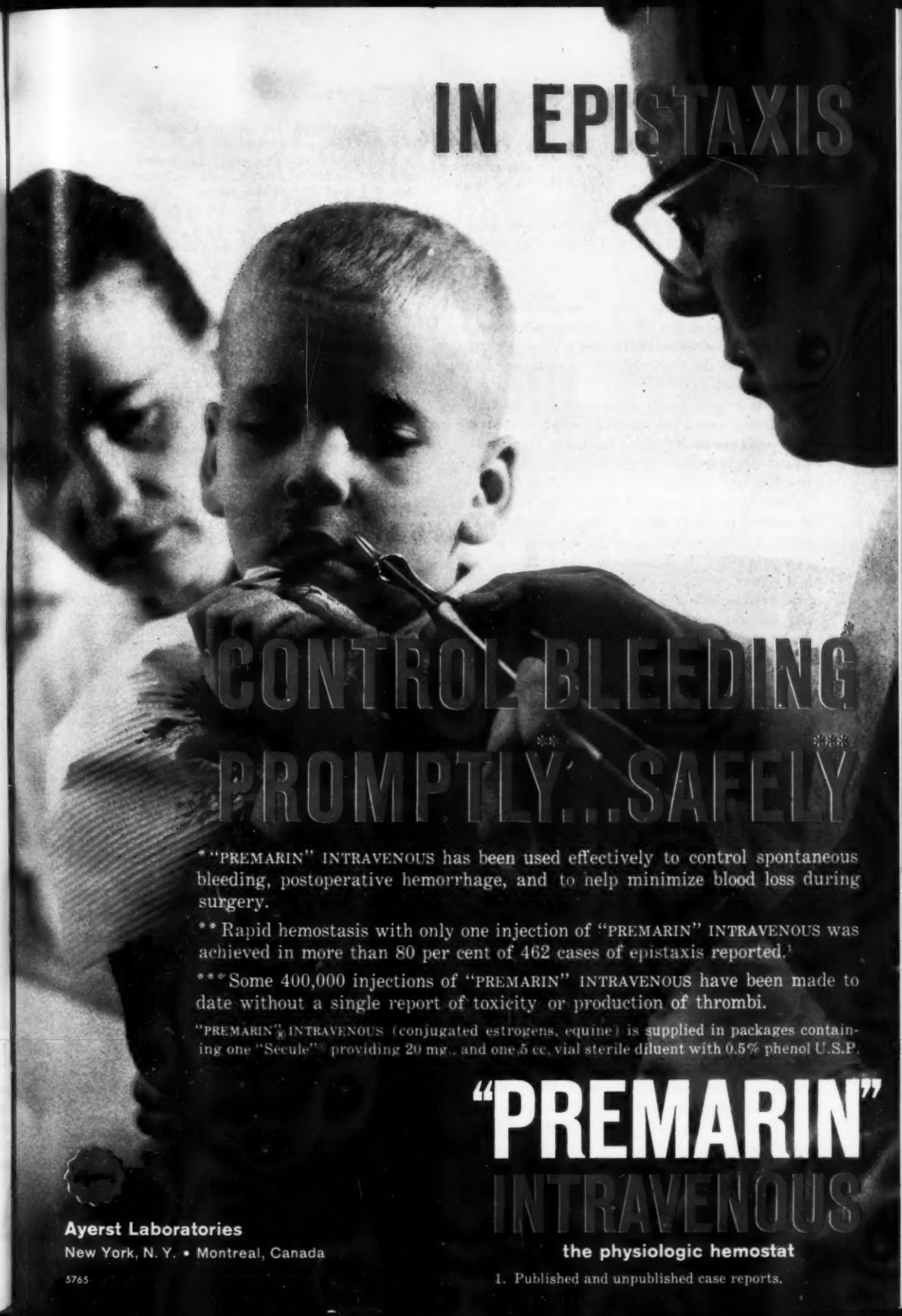
Apparently contraception may become a major issue in the political campaign of 1960. Dr. Guttmacher writes from a great background of practical experience in planned parenthood. He lists proved and disproved methods, discusses the development of such products as ENOVID® and NORLUTIN® and considers problems created by medical, religious and legal attitudes. There are chapters on sterilization, abortion, sterility and fertility, with a special chapter on artificial insemination.

The explosion in population with an increase of world population of about 17 per cent in each decade means that sooner or later something will have to be done. Certainly every physician should be acquainted with the medical problems involved, just as agriculturists are equally concerned with the provision of food.

Considering the research now going on, Dr. Guttmacher feels that his book will be dated in just a few more years, but certainly no one has better presented the present state of our knowledge and philosophy regarding contraception.

M. F.

(Continued on page A-182)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► THE MEDIASTINUM

By Ted F. Leigh, M.D., Professor of Radiology, and H. Stephen Weens, M.D., Professor and Chairman, Department of Radiology, Emory University School of Medicine, Atlanta. 246 pages, illustrated. 1959, Charles C Thomas, Springfield, Illinois. $11.50.

In the preface, the authors suggest that this book is intended for all physicians interested in mediastinal diseases, particularly those who are charged with the responsibility of diagnosing and treating diseases of the chest.

The text is profusely illustrated and the roentgenograms have been carefully selected and very well reproduced. In some instances there is excellent reproduction of roentgenographic densities that are difficult to see. The book has been written in atlas form and the subject material is presented in many short chapters, almost all of which are devoted to a single subject. The few exceptions are those cases in which the subject matter is very closely related. This individualization has the advantage of eliminating the necessity for another classification of mediastinal disease. Discussion of general considerations of some lesions is necessarily limited, but in most cases it is adequate. Special attention is given in each chapter to the roentgenographic features of these lesions.

In the first chapter the drawings and roentgenograms clearly outline the anatomy of the mediastinum. The role of radiology in establishing normal anatomy in the living subject is clearly shown by demonstration of the precise width of the posterior mediastinum. The second chapter is devoted to a simple and logical discussion of the anatomy of the mediastinal lymph nodes. In the excellent chapter on mediastinal emphysema, the authors comment that small amounts of air in the mediastinum either may not be recognized or are detected with great difficulty. There apparently are instances of mediastinal emphysema for which there is no obvious cause.

The subject of hematomediastinum, about which there is little written, is well illustrated with numerous roentgenograms. The description of the gross pathologic appearance of tumors is excellent. Also discussed are such frequently encountered structures as epicardial fat pads, which are worthy of mention for purposes of differential diagnosis.

J. R. H.

Books received are acknowledged in this department. As space permits, books of principal interest to our readers will be reviewed more extensively. Additional listings will be found on pages 454, 479 and 547 of this issue.

Drugs of Choice (1960-1961). Edited by Walter Modell, M.D., Director, Clinical Pharmacology, Cornell University Medical College, New York, with 47 contributors. 958 pages. 1960, The C. V. Mosby Company, St. Louis. $13.50.

Clinical Obstetrics and Gynecology. A quarterly book series. Cesarean Section. Edited by Edwin J. De Costa, M.D., Associate Professor, Department of Obstetrics and Gynecology, Northwestern University Medical School, Chicago. Advances in Gynecologic Surgery. Edited by S. B. Gusberg, M.D., Associate Professor of Clinical Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, New York. Vol. 2, No. 4. 304 pages, illustrated. 1959, Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. $18.00 per year.

Parkinson's Disease; Its Meaning and Management. By Lewis J. Doshay, M.D., Columbia University College of Physicians and Surgeons, New York. 224 pages, illustrated. 1960, J. B. Lippincott Company, Philadelphia and New York. $1.45.

Progress in Medical Virology. Edited by E. Berger, Basel, Switzerland, and J. L. Melnick, Houston, with eight contributors. Vol. 2. 234 pages, illustrated. 1959, Hafner Publishing Company, Inc., New York. $10.25.

Recent Advances in Public Health. By J. L. Burn, M.D., Lecturer in Public Health, University of Manchester Faculty of Medicine, Manchester, England. Ed. 2. 370 pages with 54 illustrations. 1959, Little, Brown & Company, Boston. $10.00.

Arthritis; Medical Treatment and Home Care. By John H. Bland, M.D., Associate Professor of Clinical Medicine, University of Vermont College of Medicine, Burlington. 208 pages with 39 illustrations. 1960, The Macmillan Company, New York. $4.95.

From Magic to Science. Essays on the scientific twilight. By Charles Singer. 253 pages with 108 illustrations and 14 plates. 1958, Dover Publications, Inc., New York. $2.00.

Elongation Treatment of Low Back Pain. By George H. Hassard, M.D., Department of Physical Medicine and Rehabilitation, Veterans Administration and University of Oklahoma Hospitals, Oklahoma City, and Charles L. Redd, P.T., Physical Therapist, Owens-Illinois Glass Company, Alton, Illinois. 78 pages with 47 illustrations. 1960, Charles C Thomas, Springfield, Illinois. $4.50.

Modern Nutrition in Health and Disease. Edited by Michael G. Wohl, M.D., Chief of Human Nutrition, Division of Biological Chemistry, Hahnemann Medical College and Hospital of Philadelphia, and Robert S. Goodhart, M.D., Scientific Director, The National Vitamin Foundation, Inc., New York, with 59 contributors. Ed. 2. 1,152 pages with 75 illustrations. 1960, Lea & Febiger, Philadelphia. $18.50.

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DR. Pepys' Pages

Personal Diary
and Observations on
Medical Life
by MORRIS FISHBEIN, M.D.

Feb. 1—At noon to the Belmont Hotel for luncheon with Edward J. Sparling, president of Roosevelt University, William J. Quinn, president of the Chicago-Milwaukee Railroad, and Mesdames Samuel Horowitz and Louis Binstock, and after that to speak to a thousand women of many faiths in an annual interfaith day. And these occasions are altogether most productive of understanding. In the evening to the opening night of MacLeish's play "J.B.," which is the Book of Job transferred to modern characters—a play that is sad indeed because the torments and tortures of living would seem to make man lose his faith and he is continually asking Why?, without an answer. The only lesson that MacLeish finds in this Pulitzer prize play is that we must accept whatever life brings and that living is its own reward.

Feb. 2—To the dentist for minor repairs and major gossip. Then came Dr. DeNosaquo for an interview on current events in the drug industry. Reading now Irwin Shaw's "Two Weeks in Another Town," and he writes magnificently of life in Rome in the movie colony, with an excellent picture of the night life of that gorgeous city, yet somehow it is a capsulated play of what might have happened just as well in Hollywood or New York. In the evening to the Hall of Fame of the International College of Surgeons where Philip Lewin spoke of the history of orthopedic surgery with numerous slides, recalling Porter, Ridlon, Putti, Hugh Owen Thomas, Abbott, Albee and many more. Old Pepys introduced and paid tribute to Max Thorek.

Feb. 3—Dr. George Wied to confer on the problems of *Acta Cytologica* and we evolved some interesting solutions. In the afternoon to the funeral of S. DeWitt Clough where were Volwiler, Thayer, Downs and many others of the staff of Abbott Laboratories, DeBoer, Rudolphy, Sid Strauss and all the staff of the Chicago Heart Association, with which he worked with such dedication. In the evening with the Friedells to celebrate the twentieth birthday of Morris F. Friedell, who continues to progress in mathematical employment and in sociologic study. Later to view on television a production of "The Tempest," with Maurice Evans and Roddy McDowell, and having enjoyed this Shakespearean play so frequently on the stage wondered how it can be made so dull on television.

Feb. 4—At my stint with the periodicals. In the evening to hear the symphony with "Scheherazade," and Boris Janis playing Liszt and everybody loved it.

Feb. 5—At noon to lunch with Pat Page, Fanny Butcher, Al Kelly and Mesdames Hirschl and Upton, who were in my class of 1910 at the University of Chicago, to plan for our fiftieth reunion. Next to the A.M.A. to see Oliver Field and get some slides for a lecture on quackery. So met also George Hall and many of the personnel of a decade ago.

Feb. 6—To visit Justin, who just returned from traveling with Senator Kennedy on his Indiana tour, and heard how the senator's family provided a Convair for the whole entourage. Next to the Michigan Shores Club, where William W. Bauer and his lady celebrated a fortieth anniversary, and greeted George Lull, Frederick Jung, Johnson Hammond, Tom Hull and Floyd Wergeland, who runs the Medicare program. Then in the snow out to the Moraine Hotel to dine with the Marks family, the twins dancing and performing gymnastics.

Feb. 7—All the day at editing and in the evening to dine with the Isa Kahns, and here much talk of travel and retirement, for most of those here gathered have retired and travel. So played at bridge and gin, being quite efficient in both.

Feb. 8—At noon to the board of the Lyric Opera, and heard of the great plans for the new season and how the stars have multiplied fees to astounding figures.

Feb. 9—All the morning with the gentleman representing Uncle Sam's Department of Internal Revenue and learned a great deal about my business and his. Reading "Perspectives," a "think" magazine of biology and medicine. In the evening to dine came Ernie and Sylvia Klein, and we talked of travel as they begin a tour around the world.

Feb. 10—All night the snow poured down to blanket Chicago and all the Midwest, so remained indoors. In the evening to the Congress Hotel, where the Variety Club made Irv Kupcinet "man of the year." Here were Russ Stewart, Emmett Dedmon, Jack

(Continued on page 188)

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en with kishki. Thereafter to the Society of Medical History, where Ilza Veith presided to a crowded room and old Pepys told the tale of the rise of quackery and Fred Stenn reviewed the history of the McCormick Institute for Infectious Diseases, making altogether an intriguing evening.

Feb. 18—At noon to speak for the Johanna group of the United Order of True Sisters, which is a wonderful group of middle-aged and elderly women who for many years have been contributing sums to medical charities. Spoke to them of medical progress, being introduced by Mrs. William Margolis in a fine, succinct statement. In the evening to dine with the Jackson Park branch of the Chicago Medical Society, seeing such old friends as G. H. Mundt, Halstead and many of the faculty of the Billings Hospital. The speaker, Professor Robert F. Borkenstein of Indiana University, told of the technic and results of the polygraph, usually called the "lie detector," and demonstrated on Dr. Gingold the inability of the subject to conceal the truth even with experience in the operation of the device. And present also were the captains in charge of the police and many of their assistants and associates, all of whom, Chicago being what it is, may ultimately find themselves in the subject's seat.

Feb. 19—The snow pours down and all the populace goes into hibernation. Influenza strikes multitudes and each day more Chicago policemen are associated with the pilferers. Read a terrific mystery by Noel Clad called "The Savage," and also an amazing series of lectures by Wilder Penfield and Lamar Roberts called "Speech and Brain Mechanisms."

Postgraduate courses are valuable, but for the keen man the ability to treat his patients when necessary in hospital and the possibility, if he so desires, of being able by hard work to become a consultant will keep him abreast of current medical thought far more than any number of lectures and demonstrations. The rusty general practitioner and the stale consultant will always create a problem: they are the fruit of isolation and lack of interest. If the two great branches of the profession can come together as equal partners in the wards of the hospital, as they do (only too rarely) in domiciliary consultation, it will become difficult for members of either branch to feel lonely or to lose interest.—*Journal of the College of General Practitioners.*

* * *

At noon to the Tavern for luncheon with President Sparling of Roosevelt University discussing new developments, and happy to hear that the Auditorium Opera House is to be rehabilitated, for it was always my ideal of what an opera house should be. In the afternoon to hear Rosalyn Tureck play Bach with the symphony orchestra and it seemed to be like a glorious practice session in arithmetic; my delight was the full orchestra in the Bartok "Suite From the Miraculous Mandarin."

Feb. 20—More snow and spent the day in writing and editing and read again "Gracian's Manual," translated by Martin Fischer. Here are a few quotes:

"He hazards defeat who plays with cards exposed."

"To be a man of many sides, is to count as many men."

"Many have been made through the greatness of their enemies."

"A courteous way of saying No is to change the conversation."

And from the psychiatrists:

They had been for several years in the retreat and each day they used to meet to exchange confidences.

"I have decided to speak today in the Forum," said one. "The world will long remember what Julius Caesar said today."

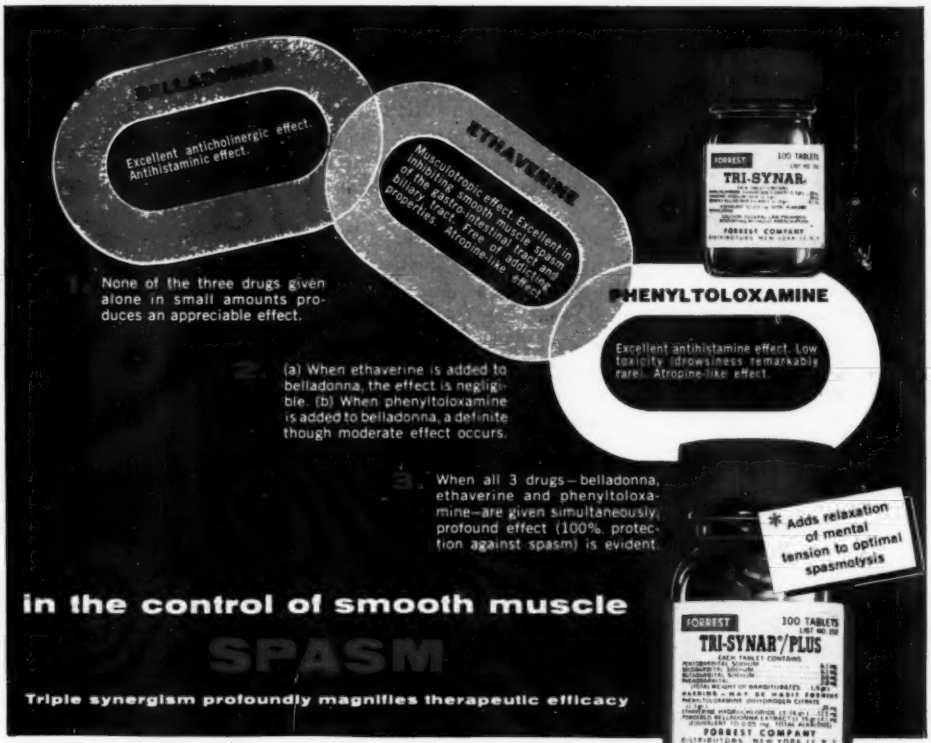
"Well, Julius, if I were you," said the second, "and incidentally I am. . . ."

Feb. 21—Still more snow, and hibernating like all the rest. Again working on ophthalmic tumors and cardiologic manuscripts and read a new work of diction by a young writer who wants an opinion. Enjoyed particularly a study of Chile reported on TV.

Feb. 22—All this day at the desk which made it a good day to work because there was no mail—Uncle Sam resting on Washington's birthday and making up for it with Lincoln's. Reading John Chapman's review of the theater for 1959 called "Broadway's Best," and found it difficult to enjoy synopses of plays that I had seen since the synopses are so inadequate compared to the actual performance. Reading also Mac Greene's "Year Book of Drug Therapy," edited by Harry Beckman, and it is absolutely full of important abstracts of articles about the newer drugs and other preparations which actually come so fast that even a year book cannot be abreast of them. The occasional editorial comments of Dr. Beckman are worth all the cost of this contribution. In the evening Mistress Pepys off to sit with the research committee of Michael Reese Hospital.

Feb. 23—More snow, and in the evening to the Hall of Fame of the International College of Surgeons where came a multitude to hear old Pepys describe medical bookplates. Here Philip Thorek presided, Ed Compere introduced old Pepys, and the bril-

(Continued on page A-192)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INDICATIONS: Spastic and functional conditions of the gastrointestinal tract (including spastic colitis, epigastric distress, adjunctive therapy in peptic ulcer, spastic constipation), biliary syndrome (dyskinesia, cholecystitis), primary dysmenorrhea, vomiting of pregnancy, dysuria and mild ureteral spasms. **CONTRAINDICATIONS:** Glaucoma, lower urinary tract obstruction, or pyloric obstruction due to stenosis or scarring.

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liant audience included a deputation from the American Dental Association, another from the school of pharmacy of the University of Illinois, and members of the honorary fraternity of pharmacy, and altogether a fine occasion.

Feb. 24—By plane to Phoenix to the Arizona Biltmore, reading en route "Wicked Women," which Lee Wright edited, being mystery stories by great writers in which women have done the crime. Finished "Necessary End" by Anita Rowe Bloch, which is the best picture of what happens in a family sociologically and psychologically when the father gets a coronary thrombosis. And with all this a fine account of the drug industry.

Feb. 25—Lay late reading Richard Llewellyn's "Up, Into the Singing Mountain," about the Welsh in Patagonia in the Argentine, a good story full of local color. So played at golf with Mistress Pepys in the Arizona sunshine and met Modie Spiegel and Dave Silverman of Chicago, and Max Schuster and many others here for winter relaxation.

Feb. 26—With Mistress Pepys walked up the mountain toward the reservoir and down again. For luncheon came Harold Swanberg and his lady from Quincy to talk of the American Medical Writers' Association and the Society for Academic Achievement. In the afternoon again at golf. In the evening came Bill and Stanley Lasdon and the ladies after a long ride from New York—eight hours on a DC 6. So chatted of this and that and then to bed.

Feb. 27—To play at golf with the Lasdons and not playing too well. In the evening to dine and played gin till late in a five-handed game and lost a little.

Feb. 28—Up early to play golf with John Garlock, surgeon from New York, and the Lasdons. So found myself with a bursitis in the elbow, but it did not interfere with my skill at gin, played in the sunshine beside the pool. In the evening to dine with the Conns and Wolfes at the Century Club, with Adlers, Basch and many more from Houston, Lincoln and Detroit, for this is a happy hunting ground.

Feb. 29—Early to walk the mountain road, then lunch at the pool and mathematics with Armour, Friedman, Garlock and Lasdons, and old Pepys so good he merits a diploma. Then dined and danced and finished Coulter's "Damned Shall Be Desire," a fascinating novelization of the life of Guy de Maupassant.

RICHARD ARMOUR

SUNDAY

Sunday is, or so it's said,
A day for staying late in bed,
For letting whiskers grow and harden,
For cultivating home and garden,
For reading books, both gay and boresome,
For golfing with the good old foursome,
For eating snacks and sipping slowly,
Relaxing pleasantly and wholly.

And Sunday is of course the day
When patients have a fiendish way
Of getting fingers caught in mowers
And running head-on into doors
And getting beaned upon the links
And passing out from poisoned drinks
And keeping thus, with zeal and zest,
The doctor from his day of rest.

RASH REMARK

Consider the bothersome, ugly skin rash,
The crusty thick or the blushing thin rash.
It may be something the patient ate,
It may be caused by the patient's mate,
It may be nerves and it may be weather
(For human skin isn't tough as leather),
It may be psychotic, or even prenatal,
But remember this: it is never fatal.

It may cause itching, it may look bad
And embarrass the hell out of some poor lad,
It may mean scratching a certain place
That's hard to get at, in public, with grace.
But here's the prognosis you've got to give:
"Whether you want to or not, you'll live."